March 27, 2017

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, Maryland 20852

Attention: Docket Number FDA-2015-D-2537

Subject: Submission of Quality Metrics Data; Revised Draft Guidance for Industry

Dear Sir or Madam:

The International Society for Pharmaceutical Engineering (ISPE) would like to submit comments on Docket Number FDA-2015-D-2537, **Submission of Quality Metrics Data, Revised Draft Guidance for Industry, associated Federal Register Notice (FRN), and webinar.** ISPE is an individual membership Society of more than 18,000 professionals involved in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.

Given the high number and extensive range of comments, explanation of the structure of our response is considered necessary:

- Section I contains ISPE's key messages.
- Section II, Background, summarizes ISPE's learnings and findings from its four-year Quality Metric Program
- Section III, Main Comments and Recommendations, provides a summary of ISPE comments and gives ISPE recommendations for simplifying the proposed program to help increase the value for FDA and industry.
- Section IV, Collated Comments, is intended to expand explanation of the summary comments given in Section V and provide an ISPE collation of members' detailed comments given in Section V.
- Detailed Comments from ISPE members with reference to line numbers in the draft revised guidance are given in Section V.

ISPE appreciates the opportunity to submit these comments, and welcomes future dialog with the Agency.

Sincerely,

John E. Bournas
ISPE CEO and President

ISPE wishes to recognize and thank FDA that comments made in response to the 2015 Guidance, Request for Quality Metrics and associated Federal Register Notice (FRN) have been considered when producing the revised draft guidance, Submission of Quality Metrics Data, revised associated FRN and supporting webinar. It is pleasing that FDA has included some major comments from ISPE [1] in the revised guidance such as:

- A phased introduction with an objective of learning and evolving
- Starting with three recommended metrics
  - Lot Acceptance Rate
  - Product Quality Complaint Rate
  - Invalidated Out of Specification Rate
- Introduction of the option of site-based reporting

I. Key Messages

ISPE continues to support a quality metrics program that has value to FDA, industry and patients.

ISPE comments on the revised draft guidance are extensive and have led ISPE to conclude that the program, based on our analysis, as proposed has low or no value and the burden is substantial. Consequently, ISPE recommends that FDA issues a final guidance for a carefully structured FDA pilot program before such the program commences. We suggest that such a limited pilot program and associated guidance should be designed and agreed with industry representatives to clarify requirements and value relative to the burden. The pilot program should have a limited duration of data collection, followed by an analysis period and dialogue with industry. It is recommended that common mechanisms of engagement for design of a complex scientific study are used, for example, a small but diverse group from industry works with the FDA quality metrics team to establish a structured multi-phase approach with distinct measurable goals, milestones and evaluation points. Early steps could be:

- Refine and test definitions
- Expand examples to clarify reporting approaches for all common scenarios
- Resolve technical details to achieve the required consistency within a test group
- Conduct a small-scale pilot
- Review outcomes, burden and value of the pilot and define next steps

ISPE is very willing to work with FDA to facilitate these interactions.

ISPE key comments on the revised draft guidance are:

- The proposed requirements are complex and preclude standardization due to challenges with unclear definitions, which are different to those commonly applied in industry and in ISPE Pilots programs [2,3]: metric calculations are both atypical and inappropriate
- Lack of clear and standardized quality metrics data elements will confound attempts at data analysis and will likely lead to unusable data. This will limit the ability to draw conclusions and achieve the desired benefits

- Burden is significant for companies choosing to participate in the voluntary program. The burden for a mandatory program is estimated as a minimum of $285 million total industry cost not including IT/system construction costs. This burden is due to:
    - Increased number of data elements to report and complexity of reporting, for example CMO data

  We also believe there is a high likelihood that requirements will change in the future and that further significant expenditure will be required.
- There are also opportunity costs for implementing this program as resources would be applied to a low value program and be diverted from working on other company existing Key Performance Indicator (KPI) and continual improvement programs.
- We are also concerned about the high levels of management attention that may be given to a relatively low value program, since data will be submitted to FDA rather than just used for internal review.
- We appreciate FDAs attempts to create incentives for participating in the voluntary program but have significant concerns with the Quality Metrics Reporters List concept due to:
    - The lack of relationship between simply reporting metrics and true quality performance
    - Achieving a higher tier of reporting is biased to companies with fewer products, sites and simple supply chains
    - Simply reporting data to FDA does not provide a good basis for appropriate use by providers and payers potentially leading to inappropriate questions being posed to companies
- Lack of assurance of the confidentiality and security of data submitted. For example, the guidance does not clearly state that submitted data and the metric values calculated are considered pre-decisional and thus not subject to Freedom of Information requests.

This extensive and data-driven response is consistent with all previous ISPE formal input to FDA's proposed quality metrics program such as ISPE's 2013 white paper [4], response to the FDA 2015 draft guidance [1] and Report of ISPE Quality Metrics Pilot Program, Wave 2 [2].

As an alternative proposal ISPE suggests that FDA conducts a fundamental review of what it is attempting to achieve with a quality metrics program and develops alternative approaches to a program based on industry submission of harmonized data elements. Again, ISPE is very willing to work with FDA to develop such a revised program.

II. Background

ISPE has considerable experience working on voluntary quality metrics programs. ISPE has conducted two pilot programs in cooperation with McKinsey and Company with participation from 28 companies and 83 sites. These companies and sites represented a wide range of technologies and included contract manufacturing organizations (CMOs) and laboratories, and drug substance manufacturing sites. For further information please refer to reports of ISPE Pilot Programs Wave 2 [2] and Wave 1 [3].

The findings from both these pilots relevant to the revised draft guidance are:

- Definitions are extremely important. Significant resource and attention were given in both pilots to produce definitions understood by participants to enable consistency in reporting and ability to conduct analysis.
- Many companies currently collect metric data at a site level and often utilize definitions different from the FDA or agreed ISPE harmonized definitions. Moreover, there are often different definitions or variations in interpretations of a definition between sites in the same company. Consequently, there was a burden for companies to collect data against harmonized definitions. In the ISPE pilots, this minimized burden was considered appropriate for the value companies received from the pilots.
- Producing metric data on a product basis is difficult for products manufactured with complex supply chains and for companies with a large number of products. Historically, these data were not commonly produced or included in periodic product reviews (PPRs)
- The pilot studies concluded that Lot Acceptance Rate, Product Quality Complaint Rate (PQCR) and Invalidated Out of Specification (OOS) Rate (IOOSR) have potential value using the ISPE definitions (definitions are given in Wave 1 and 2 Reports [2,3]), and consequently should be studied further.

III. Main Comments and Recommendations

Based on comments given in Sections IV and V and using ISPE's experience ISPE recommends that the FDA voluntary program be conducted as a limited pilot and be further simplified and carefully structured to be more focused on desired objectives and benefits. Such simplification would clarify the program, reduce the burden and so encourage more participation in this phase giving a greater opportunity to realize benefits and provide learning. A final guidance should be issued before data collection under the limited FDA pilot program commences to maximize the likelihood of collecting useable data.

The following recommendations are for consideration, discussion and agreement as part of an engagement process before the FDA pilot commences.

1. **Objectives.** The currently stated objectives (e.g. guidance, lines 18 to 22 and FRN, section I Background, page 7) are broad and the criteria are not clear enough to assess if objectives are achieved.

   Recommendations

   Some suggestions for more focused objectives are:

   - To establish practicality of operating a harmonized data collection and calculation system across companies and complex supply chains, and with CMOs and API manufacturers
   - To estimate how quality metric data could be linked with other factors to influence inspection frequency, for example as a first step:
     - To test the hypothesis that Lot Acceptance Rate and Product Quality Complaint Rate are related to a site or company quality performance and product quality, and that Invalidated OOS Rate is related to laboratory quality performance
   - To develop proposals using industry experience regarding how quality metrics could assist with implementation of state-of-the-art, innovative quality management

systems for pharmaceutical manufacturing, for example, use of the calculated metrics as an element of the post approval manufacturing change reporting program with an emphasis on encouraging lifecycle manufacturing improvement.

As a further suggestion, the scope should be adjusted so that a subset or subsets of companies or sites are encouraged to submit data elements for less than 100% of their products, for example 5 products per site. This would reduce the challenge and burden of submitting data for all products and be in accord with the revised objectives. A standard number of products per site may allow cross-site comparisons.

2. **Definitions.** Many of the terms and definitions of data elements (e.g. "saleable lots" line 267) and metric calculations (Invalidated Out of Specification Rate (IOOSR), lines 225 to 229) are:

   - Atypical and different from those commonly used in industry
   - Different from the ISPE-proposed definitions, which were used in ISPE Pilot programs and could be considered a starting point for industry-harmonization
   - Not sufficiently clear despite exemplification in the guidance
   - Open to interpretation due to the use of non-standard atypical definitions

   The lack of clarity on definitions is especially problematic for CMOs who could be requested to structure data differently for each of their clients. A senior leader from a CMO has said that we "need better clarity on definitions – otherwise we will be requested to provide data the way each sponsor has structured it"

   A summary of major comments is given the table in Section IV, sub section 2.

   Challenges with different and unclear definitions and inappropriate metric calculations lead to:

   - Inability to compare metric values between time periods and sites/companies/ technologies due to wide variation in data element values
   - Inability to make logical conclusions or derive potential relationships, for example with IOOSR and hence
   - Low or no value with benefits not realized
   - Burden to change definitions for example training staff, changing IT systems, negotiating quality agreements with CMOs, both for the current program and if changed again in future
   - Inappropriate allocation of resource to a relatively low value program which subtracts from existing KPI and continual improvement programs which have been designed to have value for a site/company
   - High level of management attention distracting from other activities that offer more perceived value

   Recommendations

   Definitions should be clarified and examples made even clearer to help participants. This should be completed as part of an engagement process before companies commence data collection. It is recommended that ISPE definitions are considered, which at high level are given below. For full detail of ISPE definitions please refer to ISPE Pilot Wave 2 Report [2]:

- Lot Acceptance Rate per finally dispositioned lots = Number of lots released divided by the number of lots dispositioned in the reporting period (see Wave 2 Report [2] for alternative name for 'dispositioned')
- Product Quality Complaint Rate = Number of product quality complaints received divided by the total number of packs released. A different denominator is required for API manufactures, for example kg or this metric should not be calculated for APIs
- Invalidated OOS Rate = Number of Invalidated OOS divided by number of tests performed

3. **Reporting of Data.** There are many comments such as:

- The number of quality metric data elements increased. There are 11 (lines 265 to 365) in this guidance compared with 10 mandatory quality metrics data elements in the 2015 draft guidance.
- How data should be reported (Appendices in the draft FDA guidance). Proposals seem complex and potentially burdensome because proposals are different to how companies currently collect data.
- Reporting values by quarter adds to the complexity and burden. It is estimated the burden would be 34% reduced for annual reporting compared with quarterly reporting (see Appendix 1).
- There is increased burden to collect 11 quality metrics data elements as in the 2016 revised FDA draft guidance, which is estimated as 19% increase per product compared with the 8 data elements in the 2015 draft guidance required for the same three proposed metrics – see Appendix 1. In total, there are 25 data elements total per product to report – 11 quality metrics data elements plus 14 identifying information data elements.
- Using assumptions given in Appendix 1, it estimated that approximately 1250 FTEs, equivalent to $190 million would be required to collect and submit 11 data elements for a relatively simple supply chain for 63,000 product reports. API reports could add a further estimated $95 to $150 million and this does not include significant IT infrastructure upgrade costs.
- The complexity of reporting data elements is shown in Appendices 2, 3 and 4 below. Appendix 2 is a schematic of data elements required for a single product report. Appendix 3 shows a supply chain for a 'typical' product showing two API suppliers, two finished drug product manufacturing sites and one CMO. Appendix 4 shows a complex supply chain, which involves four API manufacturing sites, two finished dosage form manufacturing sites, each using a contract testing laboratory, two in house and one CMO packaging and release sites with two further stability testing laboratories. This complex supply chain could be established to increase drug supply (prevent drug shortage) and/or act as flexible capacity for seasonal demand. The complexity could be summarized by simply looking at the number of quality agreements that will require review, likely change and re-negotiation, and establishments from which to pull data as shown in the following table:

Example	Number of Quality Agreements	Number of establishments
'Typical'	3	5
Complex	9	12

The total estimated burden per site or company will depend on the number of products.

- Reporting for a calendar year (line 405) at a fixed time different from a product's PPR cycle produces burden
- How to use the commenting process and how frequent comments should be made (line 303, 380-381). The commenting process is necessary but interpretation could be complex and burdensome, for example the need to comment on many data elements potentially on a quarterly basis.

Recommendations

- Collect only the 6 quality metric data elements required to calculate the three metrics requested based on the ISPE definitions.
- Data are collected as recommended in ISPE response to the 2015 draft guidance [1] at a site by product level for Lot Acceptance Rate, by site for Invalidated OOS Rate, and at product level for Product Quality Complaint Rate. This approach would minimize the burden.
- Data should be collected annually (not quarterly) in line with a product's Periodic Product Review (PPR) cycle to minimize burden. Quarterly data is too short a period for evaluation and therefore does not provide a benefit commensurate with the effort.
- A 300-word comment facility is provided per site for product reporting or 300 words per product for site reporting.

4. **Timing.** Further clarity is requested regarding the reporting period and frequency, and the time the electronic portal is open for submission of data. (FRN section II, page 13). It is recognized that FDA has verbally clarified that it would like 2017 data to be provided to the electronic portal from 1 January 2018 to 31 March 2018, however, this is not clear to reviewers of the guidance and FRN.

   Time is required, for example, in absence of a Technical Conformance guide to:

   - Interpret and establish the new definitions internally,
   - Update systems,
   - Provide training,
   - Collect data (e.g. from CMOs),
   - Review and approve data,
   - Add comments where appropriate,
   - Convert data to proper format, and
   - Submit.

   A senior quality leader quoted "If you gave me nine months I could submit 2017 data, but I cannot do it in three months."

Recommendations

- FDA should clarify the calendar year over which data are requested. With the changes FDA has made and is requested to make, time is required to allow companies to change data collection and reporting processes, etc. before the voluntary reporting period begins.
- If 2017 data are requested, it is recommended that the portal is open either for 6 months or for three months deferred for three months, i.e. starting in April 2018
- The recommended alternative is to start the program in 2018 with the portal open in 2019 for 6 months. This will allow time for engagement and further program clarification as recommended
- In addition, there should be time for FDA to complete its analysis, and there should be a further period of interaction, commenting and discussion with industry before progressing to the mandatory phase of the program.

In summary, there should be a one-time data submission period, then period for analysis with no data submitted (i.e. industry submits, FDA analyzes, there is FDA and industry review and then define what, when and how date should next be reported.)

5. **Site Reporting.** It is welcome that the revised draft guidance provides flexibility to report by site (lines 157 to 158), however, FDA states that its preference is for product reporting (line159 to 161 and FRN page 10, 2nd paragraph). Reporting by product is very burdensome for companies with complex supply chains (see Appendices 2 to 4) and a large number of products as shown in ISPE Wave 2 report [2]. The Report shows that reporting data elements for the three metrics of Lot Acceptance Rate, Product Quality Control Rate and Invalidated OOS Rate as in 2015 draft guidance using the ISPE-recommended approach is 1/3 less onerous than the FDA product-based approach. The complexity and burden of product reporting may reduce the number of voluntary participants.

   Recommendations

   It is recommended that more positive support for the option of site reporting of data as recommended by ISPE should be given since site reporting is consistent with industry established quality metric programs and consequently less burdensome. Additionally, it may have a relationship to site quality performance and, therefore, be helpful when estimating a site risk-based inspection frequency. It is unclear how product reporting will directly relate to site quality performance.

6. **Quality Metrics Reporters List.** The Quality Metrics Reporters List (lines 465 to 544) is presented as an incentive for voluntary participation. This new concept, however, raises a number of questions and concerns, most notably that a company or site's ability to report data, independent of the quality/accuracy of same data, would be published, and potentially lead to Freedom of Information (FOI) requests for data.

   The current data to be submitted has no known relationship to quality performance or compliance status, just level of participation, which would be of limited value to healthcare purchasing organizations, healthcare providers, patients, and consumers. It is unclear what the public or purchasers would do with the data. Any publication of data elements or calculated metric values could lead to substantial numbers of FOI requests and inappropriate questions to companies. Such requests could cause:

   - Misrepresentation of a company's commitment to quality

- Significant additional burden answering inappropriate questions.

In summary, during any pilot or voluntary program it must be clear to participants that data elements submitted and any metric values calculated must be confidential and not subject to FOI requests.

The proposed approach is also biased towards companies/sites with a small product portfolio with simple supply chains when compared to companies/sites with large product portfolios and complex supply chains. The challenge for companies with a large product portfolio to meet Top Tier requirements by reporting all data elements may deter them from participating. A senior executive from a large company with complex supply chains of a large number of products has said "I would rather be a non-reporter than mid tier". In summary, the Tier reporting concept is considered premature, and a disincentive that may have unintended consequences.

Recommendations

- The concept of a Quality Metric Reporters List should be deferred
- All data and conclusions should be considered "pre-decisional" at this juncture of the program and should not be made available via Freedom of Information Act requests or published externally.
- Alternative incentives are considered such as making public what a "seat at the table" with FDA could mean. Suggestions are ability to have face-to-face direct meetings with FDA in one-to-one situations or in small groups of similar companies, making information available to a participant before a larger group, and not just using large public meetings or e-mail exchanges.

7. **Working with CMOs.** Working with CMOs is extremely complex due to the need for interaction, and potentially sponsor and CMO having different systems (footnote 62, page 17 and Appendices A1 to A4). There are very likely to be new requirements to introduce new procedures and agreements, which could be time consuming and burdensome, especially for those companies with a large portfolio of products and complex supply chains. From a CMO perspective there could be a large number of clients and it is necessary to have all clients requesting the same information, not close variants of supposedly the same data elements. One CMO senior executive has quoted "there is too much uncertainty: it just keeps changing. I am going to do nothing." There are also similarities and in some cases differences between sponsors of applications and CMOs regarding how metric data should be reported. For example, some sponsors of applications consider they have responsibility for CMOs' performance and wish to report data from CMOs. CMOs in ISPE's programs indicate that they would like all metric data reported by sponsors and that CMOs do not report by site. Some sponsors, however, think that some CMOs may wish to report so that they appear on the Reporters List. There is still the outstanding issue of how to derive quality metrics associated with a CMO site to assist with planning inspection frequency for that CMO site.

Recommendations

- Clarity is recommended regarding how data from CMOs are reported and who has responsibility for doing this
- Clarity is requested regarding how FDA would assess the performance of CMOs when sponsors report data

8. **API Specific.** There are many issues similar to those for CMOs (guidance Appendix A2), which require clarification regarding how API manufacturers report data and who reports them. API manufacturers who produce APIs would wish to report their own data, potentially using data from their third parties (CMOs) if they use them. If there is a requirement for API manufacturers to link their data to drug products, this may not be possible and if it is, it will be highly burdensome.

   Recommendations

   - API manufacturers submit a site report without any reference to the finished drug products into which their APIs are included

9. **Engagement.** It is welcome that FDA has included more explanation and exemplification in this guidance compared with the previous guidance and an opportunity to provide comments (line 400). The detailed comments in Section V, however, show the high level of further questions from reviewers as the examples provided are not sufficiently clear and highlight the complexity of operating the program as outlined. Opportunities for interaction with FDA seem limited and use of e-mail has issues of:

   - Security
   - Difficulty of being clear enough with a question to allow an accurate answer
   - Time that an interaction takes, for example when clarification of a question is required.
   - Inability to have facile interactions with and between participating companies

   In conclusion, poor engagement will lead to poor understanding and inconsistencies of interpretation that in turn will lead to inability to interpret data.

   Recommendations

   Some relevant suggestions are:

   - The guidance would further benefit from a living FAQ, hosted on the appropriate FDA webpage Q&A file to address many of the questions raised in the draft guidance (many of which were raised in the previous draft) and any new common questions raised during the review of this version of the guidance.
   - Other opportunities for engagement between FDA and participants are recommended, for example:
     - Availability of a secure Helpdesk
     - Public meetings or Workshops
     - Small group of companies with similar issues meeting face-to-face
     - One-to-one/face-to-face
   - Early response to questions is extremely important so that companies can prepare for the voluntary phase of the program with clear understanding of what is required so obviating redundant work and potential confusion for FDA. This is particularly important in early 2017 if FDA moves forward with requesting 2017 data in the voluntary program.
   - Sufficient time is allowed for companies to prepare and submit data, and to allow for analysis by FDA and feedback to stakeholders before the program commences and during the program e.g. FAQ web site, helpdesk, public meetings

- Findings from the above program should be reviewed and shared with stakeholders before expanding the program. For example, FDA sharing ranges of data may allow voluntary participants to understand if there are data issues and inform FDA to assist with refining definitions and requirements.
- A further period of commenting is requested after the 2018 analysis period for industry to provide feedback on learnings from the voluntary phase and before progressing to the next phase of data submission.

IV. Collated Comments

The following are ISPE's main comments with detailed line-by-line comments from ISPE members of the revised draft guidance given in Section V.

1. Objectives

The objectives of this voluntary phase of the program are considered too broad, these from the revised draft guidance (lines 18 to 22) being:

"...to help develop compliance and inspection policies and practices, such as risk-based inspection scheduling of drug manufacturers; to improve the Agency's ability to predict, and therefore, possibly mitigate, future drug shortages; and to encourage the pharmaceutical industry to implement state-of-the-art, innovative quality management systems for pharmaceutical manufacturing."

Similar objectives are given in the FRN, page 7:

".... (1) establishing a signal detection program as one factor in identifying establishments and products that may pose significant risk to consumers; (2) identifying situations in which there may be a risk for drug supply disruption; (3) improving the effectiveness of establishment inspections; and (4) improving FDA's evaluation of drug manufacturing and control operations."

The criteria are not clear against which an assessment could be made that an objective is achieved.

1.1. It is a concern that FDA plans to use these voluntary reports for decision making (see FRN page 9: early resolution of potential quality problems, helping prepare for and direct inspections, use in post approval manufacturing change reporting program) without providing industry with an understanding of the basis/rationale for these decisions and when there are many uncertainties of definitions and reporting requirements. For example, how will FDA use the three proposed metrics, what criteria will FDA use and what will they make public for their intentions to the objectives given above in the FRN, section I Background, page 7?

1.2. What would "working with an establishment" (FRN page 9, 1st paragraph) look like from FDA's perspective?

1.3. It is unclear how product reporting will assist with risk based inspection planning. Site reports are much more valuable for determining 'operational reliability' (line 212) and 'safety risks of manufacturing establishments'. (line 122).

2. Definitions

Many of the terms and definitions are atypical, non-standard and different from those commonly used in industry. Additionally, they differ from the ISPE-proposed definitions. There is a burden and complexity to changing definitions. Any burden must be related to the value obtained from a program.

Despite exemplification in the guidance there remain many questions related to the proposed definitions. The main points are summarized in the following table with most comments not being repeated in Section V.

Term	Example line number	Definition Questions
Lot Acceptance Rate		
Saleable lots	267 270	"saleable lots" is not commonly used in industry and is not currently defined in the Glossary section. In the FDA Webinar, the definition of "saleable" lots varies depending on the role of the establishment (e.g., manufacturer/packager vs. contract packager). Clarification and additional examples are recommended.
In process and packaging product lots	278	"in-process and packaging product lots" is not currently defined in the Glossary section. Recommend counting finally dispositioned commercial lots only.
Started Lot	605 to 611	According to the "started lot" definition, in-process lots for which there is no explicit disposition decision (i.e. proceed at risk would not be counted). • An in-process lot for which there is no planned disposition decision may nonetheless be rejected based on unanticipated manufacturing issues/concerns. • Given that this in-process lot would not have been counted as a "started lot," it follows that the rejection would not be counted in the "rejection" tally. • We recommend that FDA clarify through examples its intention for counting only lots where "there will be a disposition decision."
Lot Number	555 to 557 and 587 to 590	'Batch' and 'Lot' have separate definitions. Recommend that for the purposes of this Guidance, the terms "lot" and "batch" should be considered interchangeable.
Metric Calculation	217 to 219	Lots started within a timeframe may not be dispositioned within the same timeframe, i.e., the numerator and denominator may not be on the same time scale. Recommend using the number of lots dispositioned as the denominator to align time scales.
Product Quality Complaint		

Term	Example line number	Definition Questions
(PQC) Rate		
Number of product quality complaints received	363	Request that FDA provide examples of standard types of PQC that are included/excluded within scope
	Appendix A1	Assigning an application number may not always be possible when limited information is provided by the complainant. • For example, the complainant may provide only a product name with no strength, dosage form, or lot number. • In cases where product information is limited and it is not possible to identify the corresponding application number, how should the complaint be counted?
Number of dosage units	223	The definition of "number of dosage units" requires clarification, for example: • For non-dosage limiting products (e.g., creams) the number of dosage units distributed cannot be determined. • Number of dosage units cannot be assigned easily for drug substance • It is unclear how to count multiple dose units, for example, is a metered-dose inhaler counted as one dosage unit? Recommend counting packs released for finished drug product rather than number of dosage units distributed which is a standard approach in the industry currently. Also recommend eliminating PQR reporting for APIs given the relatively low level of complaints for API manufacturing.
Scope	258	The Guidance states the following: "Product quality complaint data should be related to drugs that are imported, intended for import or manufactured in the United States". Recommend that product quality complaint data should be related to drugs that are commercially distributed in the United States
Invalidated OOS Rate		
Metric Calculation	225 to 229	The proposed Invalidated OOS Rate metric seeks to combine two separate measures. Invalidated OOSs are typical of method/lab issues. Other "confirmed" OOS typically represent process capability/process issues. These values are independent of one another and indexing one compared to the other results in lost meaning for both data elements. For example: • Comparing two sites with similar testing volumes and similar number of invalidated OOS, where one has highly capable processes and simple products and hence low number of confirmed OOS, and the other site's products are prone to high level of confirmed OOS related to process issues.

Term	Example line number	Definition Questions
		• The former will show an artificially higher Invalidated OOS Rate compared to the latter. • It is, therefore, recommended that to allow comparisons and be meaningful the denominator of this Rate should be number of tests per site rather than number of OOS values.
Number of OOS Results	339 to 340	Allowing two options for date that an OOS result is counted may produce systematic differences since some laboratories may have OOS results, which are not progressed to the investigation stage. Use of a single specified date is preferred.
Other		
Application Product	661	"application product" is not defined in the glossary
Non-Application Product	568 664	"non-application product" is not defined in the glossary

3. Reporting of Data

There are many comments and questions regarding reporting of data:

3.1. There are more quality metrics data elements (11) in this guidance than the 2015 draft guidance (10) for mandatory quality metrics. These requirements for additional data elements add to the burden for little perceived benefit

3.2. Reporting by product across the manufacturing supply chain will be extremely challenging and time consuming for companies with a large product portfolio and with complex supply chains (see Appendices 2 to 4). FDA states "*that most of the quality metrics data described in this guidance will be collected by establishments already as part of conducting the PPR*". For many, if not most companies it is not the case that the requested data elements are currently collected in PPRs to the definitions proposed by FDA. Proposals for reporting of data are complex and there are many comments and questions as given in Section V.

3.3. The proposed product level reporting with a common reporting period (i.e. a single calendar year) will significantly add to the burden for larger multiproduct sites as the data requested is non-standard and will require dedicated focused effort to gather and submit. This can be an extreme burden for multi product sites that spread PPR (APR/PQRs) throughout the year to leverage quality engineers and statistical resources. FDA recognized this phasing in the 2015 draft guidance, line 610. Current requirements/practices are to perform these at least annually; there is not a requirement today that these be synchronized to the same time period. Not only will this be an undue burden, it is likely to reduce the effectiveness of these reviews at the larger sites as the focus will be on data collection and submission for a common time period vs. more in depth assessment. In ISPE's response to the 2015 draft guidance, there was a request that metric data reporting was phased with a product's PPR cycle. In the FRN FDA is proposing a common

timeframe, however, it is not clear what may occur in a mandatory program. In both cases we recommend reporting data flexibly in line with PPR dates.

3.4. It is not totally clear whether the 300-word commenting text is for one product or site report or one data element. Assuming it is for one product or site report, there is concern that 300 words may not be sufficient to summarize comments on 11 quality metrics data elements collected 4 times per year with comments being requested on many lots starting in one period and finishing in a later period. Companies will naturally calculate their value of the required metrics and may wish to include action plans where appropriate, and these actions plans plus commentary of individual data elements will lead to text more than 300 words.

3.5. Some covered establishments will engage in activities for both CDER and CBER products and many of the metrics will not be differentiated, or otherwise would be difficult to separate out. This will likely be true for contact laboratories and contract sterilizers. What is the intent of the exclusion from the voluntary reporting phase of CBER regulated manufacturers, and if mixed data are submitted, will this pose a problem?

3.6. More clarity on how FDA plans to manage on-going data changes is required. For example, when an accepted batch becomes rejected (e.g. via a complaint and investigation) after data have already been submitted to the FDA, FDA advises to handle this via email. How will this process work exactly? How will establishments receive confirmation that the changes were made?

4. Timing

Further clarity is requested regarding the reporting period and frequency, and the time the electronic portal is open for submission of data.

4.1. While FDA has since clarified their reporting expectations during industry discussions, the guidance and FRN are not clear. Industry is unlikely to be ready to start to submit 2017 data until second quarter 2018 given that quarter 4 2017 data may have to be collected from CMOs, checked and verified etc. prior to submission. It is a standard practice in industry to offset the PPR due date by 90 days from the close of the data period. This data-gathering period could be before the comment docket has closed on the draft guidance and before final guidance would be issued. Alternatively, FDA could be expecting current data in 2018 and many companies may only be able to start in this timescale. The data requirements for submission and timescales should be clarified.

4.2. FDA intends to open the electronic portal in January 2018 and expects to begin the data analysis once the portal is closed. There is no indication in the guidance and FRN how long the portal will remain open. Given that the new draft Guidance differs significantly from the previous version, FDA should provide sufficient time between finalizing its guidance and when the data collection period starts for companies to prepare. As a suggestion ISPE requests at least 6 months' window and/or a deferral of three months so the portal opens in April 2018. The recommended alternative is to start the program in 2018 with the portal open in 2019 for 6 months. This will allow time for engagement and further program clarification as recommended.

5. Site Reporting

It is welcome that FDA provides flexibility to report by site, stating that this may be preferred if a company is unsure if all products and data will be reported via a product report. We appreciate FDA acknowledging that product-aggregated reporting may not be feasible, especially for large, complex supply chains. Some companies find product reporting highly burdensome, as FDA has defined it in its revised guidance. ISPE concluded this in its Wave 1 and 2 Pilot reports [2,3]. Inspection of Appendices 2 to 4 in the draft guidance clearly demonstrates the complexity of reporting LAR and IOOSR by product

5.1. The guidance states "*FDA believes that these quality metrics data, in conjunction with other data accessible to FDA, provide important information about operational reliability*". If "operational reliability" is equivalent to site operational ability, then it is considered that site reports are more appropriate than product reports.

5.2. Further clarification is requested regarding how a single product report will provide insight on all manufacturing sites and laboratories particularly during the voluntary reporting period.

6. Quality Metrics Reporters List

This new concept raises a number of questions and concerns:

6.1. The Quality Metrics Reporters list is related to extent of metric data reporting and not to quality performance. Without context (e.g. size of product portfolio, complexity of supply chain, size and range of products on a site) this approach to a Quality Metrics Reporters list has many weaknesses and few (if any) strengths. For example, a small, one product company or single-site drug maker may be able to supply the required information to the FDA easily and completely, whereas a large, multi-national, high product volume company with complex supply chains may not be able to. The list is likely to be biased against and significantly disadvantage large companies and complex supply chains and in favor of small companies with a simple supply chain.

6.2. Inclusion on the list is not related to objective measures of the quality of the product or quality of the site, but FDA states that the list might be useful as part of a supplier selection process and healthcare purchasing decisions. It is unclear and considered concerning as to how this can occur.

6.3. It is essentially impossible for a company or site with a large product range to have Top Tier reporting status by meeting the 'complete data' requirement as the resources necessary to achieve this should not responsibly be diverted from value adding continual improvement initiatives to a program that is under definition.

6.4. Any publication of data elements or calculated metric values could lead to substantial numbers of FOI requests and inappropriate questions to companies. Such requests could cause:

- Misrepresentation of a company's commitment to quality
- Significant additional burden answering inappropriate questions for a pilot program

7. Working with CMOs

Working with CMOs is extremely complex due to the need for interaction, with potentially sponsor and CMO having different systems (see Appendix 4).

7.1. Many sponsors wish to report metric data from their CMOs

7.2. CMOs in ISPE's Pilot programs indicate that they wish that sponsors submit quality metric data. A CMO may have a complex range of products, for example there may be some at the in-process, bulk and packaged stages of manufacture, which constitute only parts of a supply chain

7.3. CMOs want clear, consistent definitions so that they provide the same information to all their clients without the requirement for customization due to different interpretations by their clients

7.4. Nevertheless, some sponsors think there could be an incentive for CMOs to focus on site reporting so that their performance is fully and clearly visible. This could lead to duplicate reporting, for example when some clients wish to report by product and the CMO wishes to include all its product range in a site report since a CMO cannot be absolutely sure their performance will be highlighted.

7.5. It is not clear how from quality metrics data performance of a CMO could be evaluated and then related to help determine CMO site inspection frequency.

8. API Specific

There are many issues similar to those for CMOs, which require clarification regarding how API manufacturers report data and who reports them.

8.1. It is not clear who is supposed to report API data. Will finished product reporting establishments be expected to report API data for API used in the manufacture of the finished product? When should a contract API manufacturer report their data? Should both finished dosage form and API manufacturers submit data?

8.2. If an API manufacture wants to submit a site based report, should they include all products or just those for which data was not already submitted to the license holder for inclusion in a drug product report. For such APIs, how should this be reported? Again, examples of this would be most helpful.

8.3. The number of API batches imported or especially intended for import to the US is difficult to obtain for all types of APIs, and particularly for generic APIs.

8.4. Clarity is required on which establishment reports API stability OOS data points – there is ambiguity in the draft guidance.

V. ISPE Detailed Comments

Detailed line-by-line comments from ISPE members are provided following the Appendices and References.

Appendix 1 Burden Estimates

Data from ISPE Pilot Program Wave 2 [2] can be used to estimate and compare burden values between requirements in the 2015 FDA draft guidance and 2016 FDA revised draft guidance. In Table A1 the data elements used in the 2015 draft guidance calculation are given in the left-hand column. In the middle column are the data elements required to calculate the 2016 revised draft guidance metrics and in the right column are the data elements actually requested to be submitted in the 2016 revised draft guidance

A1: Lists of Data Elements in 2015 and 2016 FDA Draft Quality Metrics Guidances

2015 Draft Guidance Set of Data to Collect 8 Data elements	2016 Draft Guidance Metrics as Described 6 Data elements	2016 Draft Guidance Full Set of Data to Collect 11 Data elements
Product quality complaints Lots attempted which were released	Product quality complaints Dosage units distributed	Product quality complaints Dosage units distributed
Invalidated OOS results due to lab error Total OOS results Total tests	Invalidated OOS results Total OOS results	Invalidated OOS results Total OOS results Total tests
Specification – related rejected lots Lots attempted Number of attempted lots pending disposition for >30days	Lots accepted Lots started ,	Saleable lots started for packaging Saleable lots released for packaging Saleable lots rejected for packaging Number of lots started of in-process and packaging lots intended for distribution Lots in-process and packaging released packaging released Lots of in-process and packaging rejected

The 2016 Draft Guidance lists 3 metrics to be calculated – however the data listed for collection include some further data elements (e.g. separate for formulation and packaging)

In Figure A2 estimates are given for amount of effort required to collect quality metrics data elements for **one product** as given in the 2015 draft guidance and data elements in the revised 2016 draft guidance. Estimates for eight data elements in the 2015 draft guidance are given in the left-hand column. The middle column gives estimates for the effort to collect the 6 data elements used in the calculations of the requested metrics in the revised 2016 draft guidance whilst the right-hand column gives an estimate of effort to collect all 11 data elements requested.

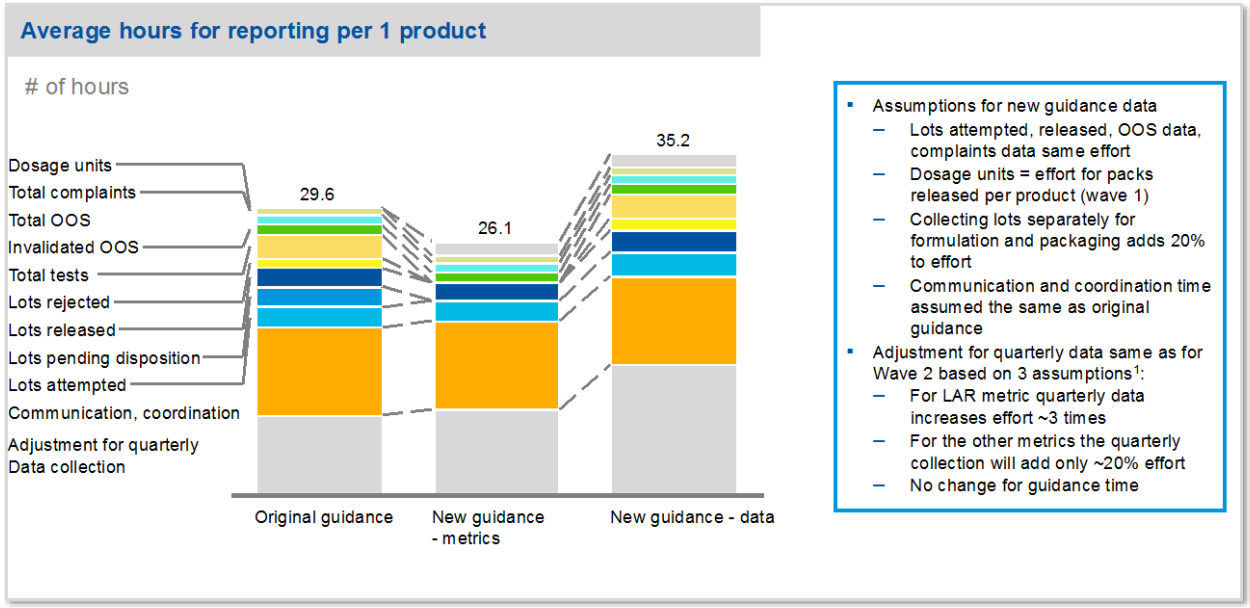
Figure A2 contains some assumptions:

- Effort for lots attempted = effort for lots started for packaging, and lots started for in-process and packaging; lots released; and all OOS data elements;
- Product quality complaints data are same effort as found for Waves 1 or 2
- Dosage units effort = effort for packs released per product (from Wave 1)
- Collecting lots data separately for in-process (formulation) and packaging adds 20% to effort
- Communication and coordination time is assumed the same as original guidance

- Adjustment for quarterly data is the same as estimated for Wave 2 based on three assumptions (from McKinsey POBOS experience):
    - For Lot Acceptance Rate metric quarterly data increases effort ~3 times
    - For the other metrics the quarterly collection will add only ~20% effort
    - No change for guidance time

For more detail, please refer to ISPE Quality Metrics Initiative, Quality Metrics Pilot Program, Wave 2 Report, Section 5.2 [2]

A2: Data Collected in 2016 Revised vs. 2015 Original Guidance



1 Informed by the POBOS experience with repeat data collection at same site over years
SOURCE: ISPE Quality Metrics Initiative

Data collection effort is estimated to be lower to collect 6 quality metric data elements for the revised 2016 draft guidance set of metrics compared with 8 in the 2015 draft guidance, possibly due to the difference in number of data elements. To collect all 11 quality metric data elements required in the revised 2016 draft guidance is estimated, however, to be per product 19% higher per product than the estimate for 8 data elements in the 2015 draft guidance. Observations regarding these data are:

- The increase in total effort is due to the high number of data elements and the request for quarterly collection of data
- Collecting data for only the six data elements used in the calculation would reduce the burden by 26% compared to collecting all 11 data elements in 2016 draft guidance and by 12% compared to equivalent 2015 guidance data elements
- Collecting six data elements for the three requested metrics at annual intervals as recommended in the ISPE response to the 2015 draft guidance [1] is estimated to reduce the burden by 34% compared to quarterly collection of 2016 draft guidance data elements

- All estimates of burden are per single product and the total estimated burden per site or company will depend on the number of products.

To calculate an estimate of the total industry burden a value of 63,000 product reports is used as was given in the 2015 FRN, Table 1 [5]. From Table A2 35.2 hours are estimated to produce one product report. Hence 63,000 products would require an estimate 2.2 million hours of effort, which translates into:

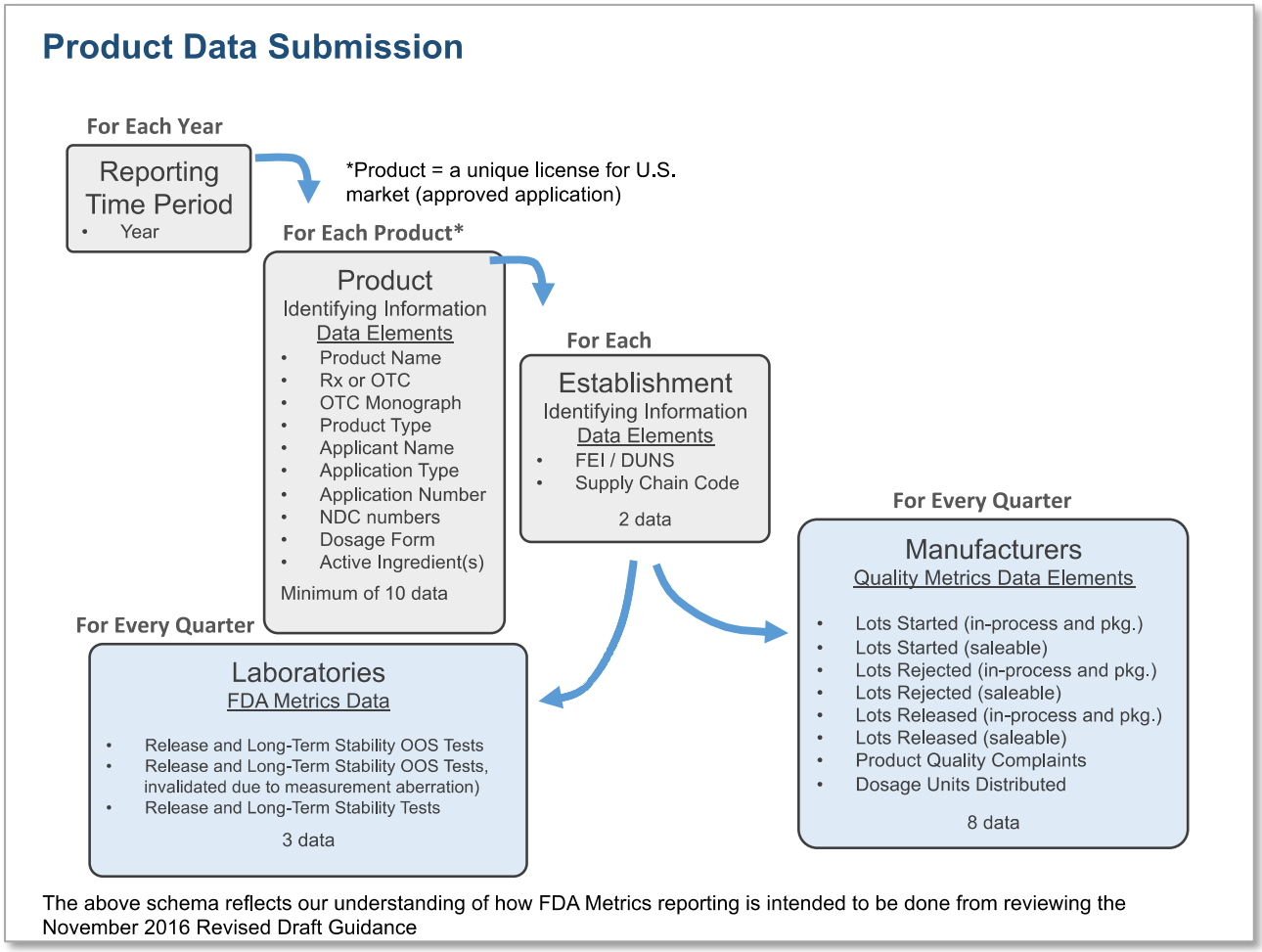
- 1250 FTEs (1750 hours per FTE per year)
- $190 million total using a value of $150,000 per FTE per year

These values do not include APIs. The number of API reports is hard to estimate from the 2015 FRN. Many API manufacturers supply an API to multiple drug product manufacturers and conversely many drug product manufacturers dual or more source their APIs – see Appendices 3 and 4. An assumption could be a range of 0.5 to 0.8 API reports to one product report making a total of 31,500 to 50,400 APR reports. APIs could add a further $95m to $150m to the total industry burden, making a total in the range $285 to $340 million.

"In discussions with member companies, significant multi-million-dollar capital and expense investments are being planned in order to comply with FDA's metrics request. Such investments include system enhancements and project funding, plus on-going licenses and maintenance. Although not calculated here, the total economic impact to industry for system work alone may exceed the estimated labor burden for just for gathering and reporting the metrics."

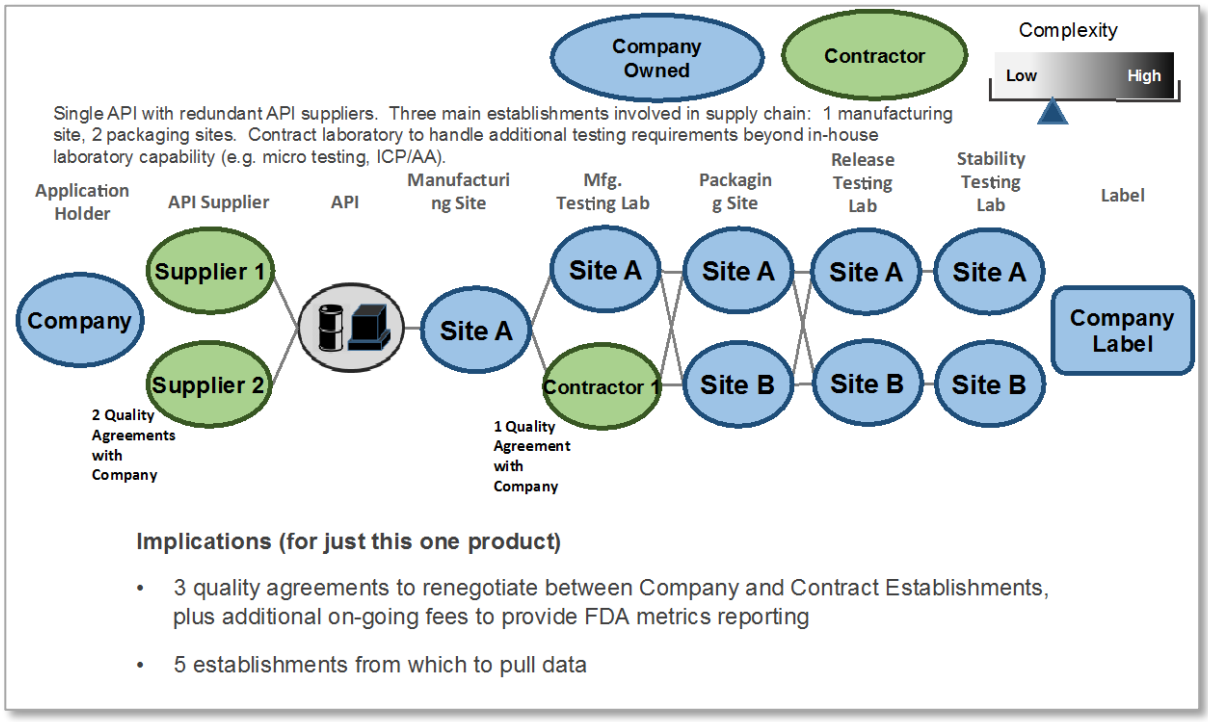
In summary, a total industry value of a minimum of $285 million from above is considered likely to be an underestimate given that the estimates to produce data elements for ISPE Wave 2 used self-selected, relatively straightforward products and hence the complexity associated with obtaining significant amounts of complex data, for example from CMOs is not included. Also, this does not include IT enhancement costs

Appendix 2: FDA Metrics Reporting Schematic, By Product



The above schema reflects our understanding of how FDA Metrics reporting is intended to be done from reviewing the November 2016 Revised Draft Guidance

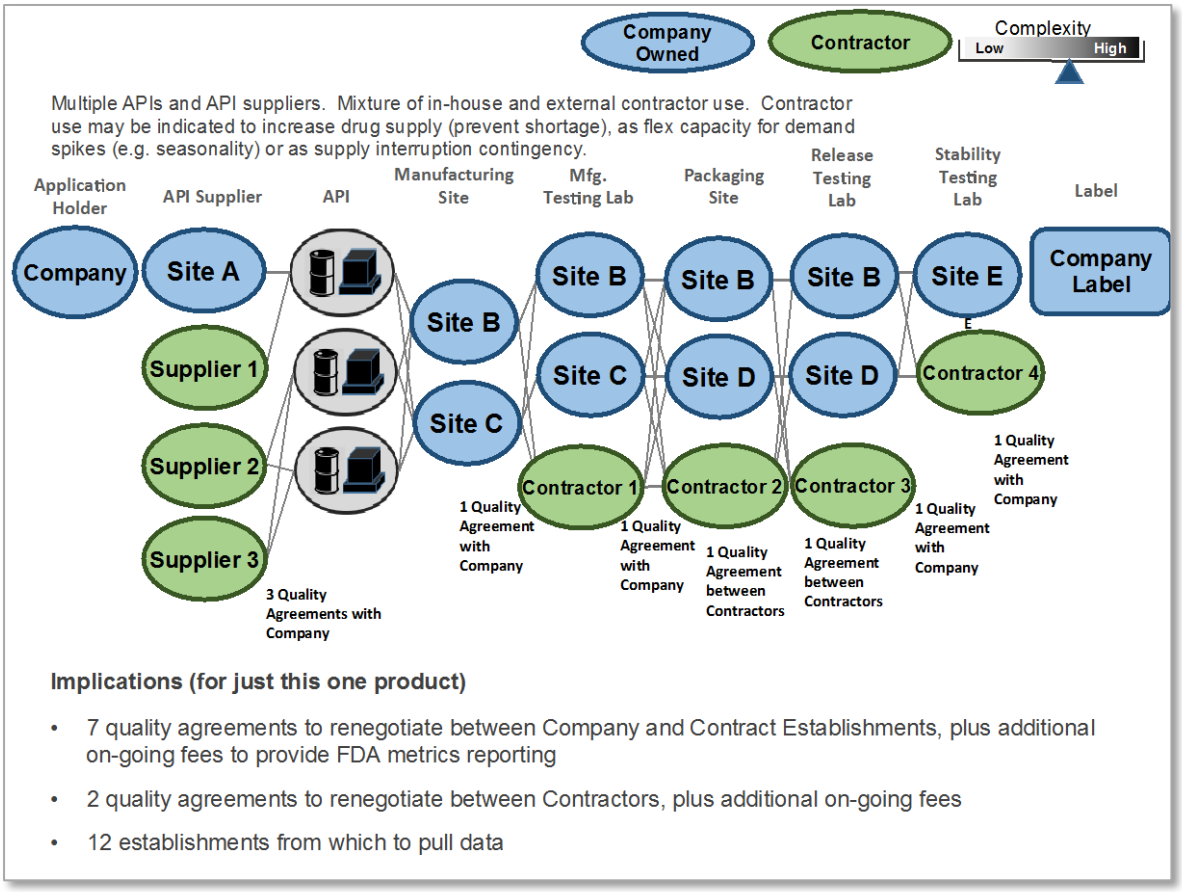
Appendix 3: FDA Example of a 'Typical' Supply Chain



Implications (for just this one product)

- 3 quality agreements to renegotiate between Company and Contract Establishments, plus additional on-going fees to provide FDA metrics reporting
- 5 establishments from which to pull data

Appendix 4: Example of a Complex Supply Chain



Implications (for just this one product)

- 7 quality agreements to renegotiate between Company and Contract Establishments, plus additional on-going fees to provide FDA metrics reporting
- 2 quality agreements to renegotiate between Contractors, plus additional on-going fees
- 12 establishments from which to pull data

References

1. ISPE response to the FDA Federal Register Notice on Quality Metrics [Docket No. FDA-2014-D-2537] and Draft Guidance, Request for Quality Metrics, 24 November 2015
2. ISPE Quality Metrics Initiative, Quality Metrics Pilot Program, Wave 2 Report, June 2016. http://www.ispe.org/quality-metrics-initiative; [Docket No. FDA-2015-D-2537-0095].
3. ISPE Quality Metrics Initiative, Quality Metrics Pilot Program, Wave 1 Report, June 2015. http://www.ispe.org/quality-metrics-initiative; [Docket No. FDA-2015-D-2537-0040].
4. ISPE. "ISPE Proposals for FDA Quality Metrics Program—Whitepaper." 20 December 2013. http://www.ispe.org/quality-metrics-initiative/quality-metrics-proposal.pdf.
5. FDA Federal Register Notice on Quality Metrics [Docket No. FDA-2014-D-2537], July, 2015.

V. Detailed Comments

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
35	FDA expects a majority of voluntary reports will be submitted by finished dosage form establishments OR API establishments	It is not clear on how API sites would report in this program. Does this text mean by only one or the other, but not both?	This lack of clarity is a theme in other subsequent comments e.g. lines 167, 175
67 Footnote 8	FDA intends to accept voluntary reports with quality metrics data that are inconsistent with the metrics and definitions in this guidance,…However, as the data submitted in a manner inconsistent with the definitions and recommendations in this guidance may not be comparable with submissions from other reporters, we: (1) do not intend to include these reporters on the quality metrics reporters list, and (2) may not be able to integrate the submission of the report into FDA's risk-based inspection model.		What criteria will FDA use to determine whether the quality metrics data reported is inconsistent with the metrics and definitions in this guidance?
82-85	FDA understands that establishments involved in the manufacture, preparation, propagation, or processing of human drugs, including oversight to ensure quality, currently use quality metrics as part of the process validation lifecycle and pharmaceutical quality system (PQS) assessment. The metrics described in this guidance could be a part of such oversight.	FDA is stating its understanding, but its understanding is not totally correct and not supported by the feedback from the industry. See comment to the right.	While FDA's statement is true that establishments use quality metrics, it is important to remind FDA that industry definitions are different from FDA and between companies, and data are not collected in the way FDA is specifying. These points were made in ISPE's Wave 1 Pilot report [2].
100-102	We expect that most of the quality metrics data described in this guidance will be collected by establishments already as part of conducting the PPR.		FDA continues to state this, but has been informed repeatedly that firms **are not** currently collecting data for PPR or otherwise according to the **exact definitions** in the draft Guidance. In addition, PPR reports are not necessarily limited in scope to a single product application but may be relevant to more than one application (e.g., a product family). These changes contribute to the additional burden.
110-111	However, FDA does not intend to require the submission of information pursuant to section 704(a)(4) of the FD&C Act in implementing the voluntary phase of the quality metrics reporting program.	If FDA intends to use the data for verification activities as identified in lines 87-102 and 117-123 and the submission is voluntary, and if the data is not reported for a Firm how does the FDA intend to risk evaluate that firm? Will the data be requested during onsite inspections?	Clarification should be given to ensure data/information can be available if ultimately requested

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
112-115	FDA does not intend to take enforcement action based on errors in a quality metrics data submission made as a part of this voluntary phase of the reporting program, provided the submission is made in good faith.	Change to "FDA shall not take enforcement action based on errors in a quality metrics data submission…"	ISPE requests FDA commits rather than "does not intend" to not taking enforcement action and, therefore, encourages more participation in the voluntary part of the program. Industry would like more assurance that voluntary submission of quality metric data does not become associated with the current enforcement practices on what is considered data integrity.
		Add context explaining how errors will be identified; does the FDA intend to inspect sites with data provided during voluntary phase to confirm accuracy - is voluntary phase auditable?	If reporting by product, then submission needs to be coordinated by central location. In this scenario, will an individual manufacturing site be responsible/accountable for the entire supply chain data? What will be expected of the site?
		Reference should be given to mechanisms to correct metrics that are reported incorrectly, for example due to a human error?	Clarification should be given to ensure data meets agency's intent.
121-123	FDA intends to analyze the calculated quality metrics to support its understanding of the safety risks of manufacturing establishments and products, and as the basis for criteria it deems necessary and appropriate for allocating inspection resources.	'FDA intends to analyze the calculated metrics to support its understanding of the ~~safety~~ **quality** risks……'	The use of the term 'safety' risk could be misleading as it usually refers to clinical safety. To avoid confusion, suggest to replace with word 'quality'
		What would be the standard safety level of risk criteria for low/middle and high? What are the criteria for allocating resource for inspections?	Transparency and alignment between FDA and Industry about criteria for levels of risk and expectations according to them
149-152	Covered establishments also include (but are not limited to) contract laboratories, contract sterilizers, contract packagers and other establishments, as appropriate, engaged in the manufacture, preparation, propagation, compounding, or processing of a covered drug product or API used in a covered drug product.	What establishments are out of scope? Distribution centers, hubs?	Examples of out of scope establishments would provide a complete understanding of the scope to complement the note ("but are not limited to")
		Text should include "testing" to cover contract testing organizations (CTOs)	Clarification should be given to ensure data meets agency's intent.
156-158	This guidance describes two types of quality metric data reports: (1) product reports submitted by product reporting establishments, and (2) site reports submitted by site reporting establishments.		By providing flexibility in reporting, FDA is greatly adding to the confusion in the industry. This opens the door to duplicate reporting and complicates the decisions of application holders, CMOs, and API manufacturers regarding responsibilities for reporting data. For example, site reporting appears to give CMOs the ability to report data for products outside of the application holder's review/oversight/agreement. Other relevant comments are given below in other responses. ISPE's position is that data are collected and submitted at a site by product level for Lot Acceptance Rate, site level for Invalidated OOS Rate, and at product level for Product Quality Complaint Rate

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
158-161	We encourage reports from product reporting establishments and site reporting establishment. FDA prefers for all covered establishments to work with a product reporting establishment and report data for the covered drug product so that the product reporting establishment submits a single product report that includes data from all covered establishments.		In describing who reports for covered establishments it is still unclear how reporting to/from CMOs, Contract Labs, Contract Sterilizers, etc. would work. Potentially there is a high burden, additional cost and complexities involved with a sponsor reporting CMO data. Please confirm if this includes that a CMO data would be reported under the holder of the filed NDA. This is implied but not stated. Listening to the webinar, an interpretation is that information reported via the product reporting establishment, should not be submitted anymore via a site reporting establishment. This situation could compromise a site's reporting visibility and hence a site may also wish to submit. See other later comments e.g. to lines 166 - 201
		Is the expectation to provide one report for each product (family or NDC#)?	A single product report could have a high level of complexity if required to breakdown the data by product type and site.
		Confirm if two types of reports must be submitted or there's an option to choose report type (i.e. product reporting establishment and site reporting establishment).	Maybe a redundancy in reporting the two types. Safety risk of manufacturing would be more visible in a site reporting type
		Request that FDA provides guidance if one establishment reports data values on a product basis and another establishment (e.g. CMO/CPO/etc.) also wishes to report by site	There is potential for duplicate reporting, which could lead to redundancy and possible misinterpretation/confusion

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
162-163	Compilation of data into a single product report will facilitate data analysis and identification of product specific issues. (e.g., potential loss in supply).	Not proposing a change to the text. FDA should better understand the product-level reporting is not as easy as it assumes it is, so should continue to support site reporting as an equally good and viable option.	While we appreciate that having a company compile all its data into single product reports makes it easier for FDA in doing data analysis and identification of some potential risks, it is hugely burdensome, mostly manual work to do this for many companies in our industry. We realize that product-aggregated metrics data have certain value, particularly if it involved pushing a button to get it. This push-of-a-button approach simply is not the reality at many companies producing quality products. So, while we appreciate FDA stated preference for product-level reporting, we question its value given the very high burden involved. We encourage FDA to continue to support site-level reporting as an option. Further clarification should be given on how a single product report will provide insight on all manufacturing sites and laboratories. Will analysis be done on an aggregate or individual establishment? Not all establishments will have equal performance? What does the FDA plan on doing if they identify a product specific issue? Covered Establishment should be aware of the potential actions required by the FDA?
165ff	Submission of a product report by a product reporting establishment	There should be clarification provided that FDA expects CMOs to provide metrics to their customers, so the customers can put it into the product report. FDA should also clarify that if the CMO does this, does the CMO still need to report this data in a site report? Will this potential duplicate reporting create confusion?	Clarification should be given to ensure data meets agency's intent.
167-168	The subject of a product report will generally be a covered drug product or an API used in the manufacture of a covered drug product.'	The subject of a product report will generally be a covered drug product or an API used in the manufacture of a covered drug product. **Separate reports should be generated for each drug product and each API.**	To clarify that separate reports be submitted for drug product and API.

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
166-201	a. Submission of a product report by a product reporting establishment. b. Submission of a site report by a site reporting establishment		It is not clear if reporting by product or site is acceptable or reporting of both are required or could be supplied, for example: Line 158 - We encourage reports from product reporting establishments and site reporting establishments. Line 404-406 To facilitate the quality metrics reporters list as described in section IV.B, a defined reporting period (e.g., a single calendar year) is needed to reduce discrepancies between site and product reporting. These sections imply that both product and site reports would be submitted. To have top tier visibility as a site (for example as a single product site) within a large company, a company may wish a site to report even though its data are also submitted by the company in a product report
168-169	The report may include quality metrics data from each covered establishment within the manufacturing supply chain that has the data described in this guidance.		Clarification should be given regarding the role of a site performing quality release if that site is performed at a location that is not responsible for manufacturing or testing.
170-172	FDA believes that, as part of its responsibility for oversight and controls over the manufacture of drugs to ensure quality, one establishment will already possess or have access to all of the quality metrics data needed to submit such reports		This is in most cases **not** the current situation as details on specific data elements as defined in this draft Guidance are **not** currently requested from the covered establishments as part on quality agreements with e.g. testing laboratories. **The consequence of FDA's incorrect assumption impacts many comments and the burden of participating in the program.** See also comments for Line No. 100-102.
175-178	This establishment should combine the data so that a single report is submitted. For example, a single API may be the subject of a stand-alone product report, as APIs are often supplied to multiple customers and finished drug product manufactures often use multiple API suppliers.	Would a single report include DP and API or be separate reports?	It is not clear how a single API supplied to multiple customers would be the subject of a stand-alone product report. Appendix A.2 for API is structured according to Application Number, which implies that there would be a separate API report for each FDF (i.e., by FDF application number). In general, it is unclear how API data is supposed to be reported. Is the FDF manufacturer supposed to report the API metrics in Appendix A.2 for API used in the manufacturing of FDF reported via Appendix A.1? Or can the API manufacturer report API data independent from FDF application number?

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
		Confirm if this includes that a CMO's data would be reported under the holder of the filed NDA.	This implied but not stated.
		Further clarification should be given on how a single product report will provide insight on all manufacturing sites and laboratories.	Clarification should be given for report structure.
180 - 185	In this guidance, we refer to the covered establishments that submit product reports to FDA as "product reporting establishments." If a product reporting establishment is gathering data from covered establishments in the manufacturing supply chain for a particular product for the purpose of submitting a product report, but data is not available for a covered establishment, FDA prefers that the product report clearly identifies the covered establishment and that specific data was not received.	Revise to clarify intent. Please see comments	The intent of this request is unclear. If the intent is to shame sub-contractors for not participating, then this seems unnecessary for a voluntary program. If the intent is to highlight gaps in a reporting establishments supply chain, then this might be acceptable but should allow for masking of the identity of the specific firm. They could be listed as API manufacturer ABC or testing lab 123 as placeholders for the real firms. There is a difference between data not received from a covered establishment and data not requested from the covered establishment. How will this distinction be made in the report? FDA states to report data as "not received" if an establishment cannot supply such data. What other consequences would there be for not receiving data? Will this be considered a data integrity issue by the Agency?
			Who is accountable if the covered establishment data is not reported - product reporting establishment or the covered establishment? Clarification should be given on ownership and accountability. From the guidance it appears that reporting data as "not received" would mean that the company would not be listed on the Reporters List. FDA has established metric definitions that are not consistent with industry current practice, that are heavily burdensome, if not impossible to collect as FDA has stated in its guidance. If an establishment in full transparency and in the spirit of cooperation, provides all the data it can get, FDA will deny publication on the Reporters List, because 1 or 2 data points were impossible to collect as defined. FDA may infer from said absence from the list, that the company has poor product quality.
		Is this accurately reflected that data would not "be{ing} available". Is it more accurate to state that is was chosen not to report?	Clarification should be given to ensure data meets agency's intent.

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
187-190	FDA believes the QCU in each reporting establishment…will generally be best positioned to compile reports…	Not proposing a change to the text. See comment to right about burden.	While FDA may be right that the duty for reporting quality metrics to them will likely fall on the quality control unit (QCU), it does not mean the QCU currently is staffed, structured, has capacity or capability to do such reporting. The QCU will have a significant learning curve and added burden to be ready to report. This is particularly the case when it comes to experience using the Electronics Submission Gateway. Is the expectation the covered establishment QCU provide the data to the product reporting establishment?
192 - 201	**Submission of a site report by a site reporting establishment** If the covered establishment prefers to report directly or is unsure if all products and data will be reported via a product report, the covered establishment may elect to submit a site report. In this guidance, we refer to the covered establishments that submit site reports to FDA as "site reporting establishments." The subject of a site report is a single covered establishment. A complete report would list all covered products with associated quality metric data specific to each product manufactured at the subject establishment as described in this guidance.	FDA should provide more positive support for site reporting of data and remove preference for product reporting as the value is unlikely to be supported by the heavy burden associated with it.	FDA provides flexibility to report by site, stating that this may be preferred if a company is unsure if all products and data will be reported via a product report. We appreciate FDA acknowledging that product-aggregated reporting may not be possible, especially for large, complex supply chains. It is likely that companies will find product reporting highly burdensome, as FDA has defined it in its revised guidance. ISPE concluded this in its Wave 1 and 2 Pilot reports [2,3]. FDA by its statements has indicated they believe it may not be possible for companies to do product-based reporting completely. Given this information and supporting data, it is recommended strongly that FDA gives more support to site-based reporting. Site-based reporting has more alignment with the inspection process.
		FDA should clarify if a CMO could provide a site report if they end up giving all their product specific metrics to the customer. Some sponsors think a CMO may be concerned about having their customers report CMO data, and not the CMO, since the FDA will publish names of companies. Example, if CMO ABC decides to provide all their metric data to customers on per product basis, and CMO ABC does not issue a site report, they may not show up on the FDA's published list of firms.	CMOs manufacture products for many customers. Most of these customers will act as a product reporting establishment and will use the data supplied by the CMO to submit their product reports. If a small number of customers are unable to submit their product reports or wish to submit only site reports, this could reflect badly on the product tier rating for the CMO. It would therefore be helpful if the CMO could submit a site report to submit all data direct to FDA to ensure the tier rating of the CMO is not affected. Alternatively, the CMO could act as a site reporting establishment, but only for a few of the products manufactured at that site and not reported by the reporting establishment in a product report. **Whatever, these arrangements are very complicated for all concerned.** Clarification should be given to ensure data meets agency's intent.
199 - 201	The subject of a site report is a single covered establishment.	If a CMO provides services for multiple product owners and each take a separate approach to reporting, if a CMO wishes to submit a site report, how will it do so? Will there be potential	Clarification should be given to ensure data meets agency's intent.

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
		for duplicate reporting?	
206-211	FDA used the following selection criteria in developing the set of data that it is inviting covered establishments to submit: (1) objective data to provide consistency in reporting, (2) of the type contained in records subject to inspection under section 208 704 of the FD&C Act, and (3) a valuable component in assessing the overall effectiveness of a PQS, within reasonable limits, and in a reasonable manner, while avoiding an undue reporting burden.	while avoiding an undue burden' should be deleted	The data elements as currently defined will impose a significant burden on industry, especially those companies with a large product portfolio and global footprint. Industry provided strong, compelling feedback on the July 2015 draft guidance that FDA has grossly underestimated the burden associated with its metrics program. FDA has increased the burden associated with the revised draft guidance by increasing the number of data elements required from 10 to 11. ISPE in its Wave 2 Pilot report showed the burden to be at least 3-times higher than what FDA estimated for the 2015 guidance. The costs associated with complying with FDA's proposed revised draft guidance are high and will be on-going; which include data system infrastructure creation and on-going maintenance, increased staffing (or diversion of quality resources from QC/QA to reporting specifically for FDA), additional contract fees and renegotiation of quality agreements to enable FDA metrics reporting and others. A discussion of the burden is given in Appendix 1 of this response.
211-212	FDA believes that these quality metrics data, in conjunction with other data accessible to FDA, provide important information about operational reliability.	Confirm: operational reliability = site operational reliability --> Site reports are more appropriate than product reports	There's a need for clarification in terms of FDA objective between "safety risks of manufacturing establishments", "Operational reliability" and "product specific issues"
214-215	Using reported data described in the following section, FDA intends to calculate quality metrics for each product and covered establishment, where applicable:	Further clarification should be given on how a single product report will provide insight on all manufacturing sites and laboratories.	Clarification should be given for report structure.
		Covered Establishment should be aware of the potential actions required by the FDA.	What does the FDA plan on doing with the calculated metric? Will there be set targets?
215	Quality Metrics that FDA Intends to Calculate	There should be a comment inserted by FDA that more details on these 3 metrics and how to calculate are provided later in this document	Clarification should be given to ensure data meets agency's intent.
221- 223	Product Quality Complaint Rate (PQCR) as an indicator of patient or customer feedback. PQCR = the number of product quality complaints received for the product divided by the total number of dosage units distributed in the current reporting timeframe.'	Add a foot note that for combination products/ devices used to deliver the product, complaints should be reported at product on market level not per site involved. Direct the reader to Section III.C.(3).	See entry for lines 361-375.

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
233	Section IV.B describes the types of metrics FDA…'	Section ~~IV~~ **III**.B describes the types of metrics FDA…'	Reference in line 233 is incorrect
234-235	segmented by covered establishment, where possible	Further clarification should be given how this would be reported - despite examples and Appendix 1 and the webinar, reporting of data is not totally clear	
241-242	Data that is summed and reported as described in this section is in a readily accessible format for analysis.	No change; just a comment to FDA's statement (see next column).	FDA states that data that are summed and reported as described in its revised draft guidance and is in a readily accessible format for analysis. This is **not** the case, currently across the industry. There is a huge effort required (both initial and on-going) for companies to be able to collect, "sum", and report the data the way it is described in FDA's revised draft guidance. To assume it is already in a readily accessible format for analysis (as FDA defines the metrics) is not correct.
245-248	FDA recognizes that it may not be possible for some covered establishments to identify started lots, rejected lots and OOS results that are specific to drugs that are imported, intended for import, or manufactured in the United States	This statement is accurate so no change, but it deserves submission of a comment.	This statement is accurate, yet confirms consistent industry feedback. While FDA states in multiple places in its FRN and draft guidance that it believes these are records all establishment already keep (as basis for authority to request them), they also state in multiple places that they realize it may not be possible for establishment to collect and report these. It appears that FDA realizes, by its statements, the difficulty and burden establishments will have with complying with its metrics request, however, appears to assume that the metrics are already readily accessible. .
		Neither of the solutions provided by FDA for difficulties associated with lot reporting are desirable. A possible solution would be for companies not to be eliminated from the public reporters list by virtue of it being impossible or highly burdensome for them to segregate out non-U.S. products.	As FDA indicated in lines 245-254, segregation of lots by U.S. and non-U.S. products can be challenging, if not impossible. This is particularly the case for API, where the API supplier may have no knowledge of where its API is used by its customers, or where a single lot is split for multiple markets. In such cases, the only options provided by FDA are not desirable (1) do not report the data, thus eliminating one from being on the reporters list, or, (2) give FDA data for non-U.S. products over which it does not have jurisdiction.

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
	...if the manufacturing process uses the same process and controls data for lots that are not specific to those that are imported, intended for import, or manufactured in the United States, the report could include both data from lots not imported or intended for import to the United States with the data from lots imported or intended for import to the United States for the lot acceptance and invalidated OOS metrics	The Guidance states that "Product quality complaint data should be related to drugs that are imported, intended for import or manufactured in the United States." There is also guidance in the LAR section that allows for excluding information on lots produced for countries outside the US. There are many factors that affect product complaint levels globally including cultural differences between regions and countries. There are also challenges in obtaining accurate production coding information particularly for non-application products. This makes it difficult, if not impossible, to determine the producing location when product is sourced from more than one manufacturing site.	We recommend that product quality complaint data should be only related to drugs that are commercially distributed in the United States. This approach minimizes the impact of cultural differences and eliminates the challenges in trying to parse complaint data from other regions for US sourced products.
250-254		We ask FDA to make the reporting simpler such that burden is acceptable and difficulties are reduced, before moving forward with its program, or, at least, provide companies the time they will need to make compliance possible or less burdensome. For example, excluding CMOs, contract labs, contract sterilizers and contract packagers from reporting may reduce the difficulties FDA recognizes will exist with its proposed metrics program.	FDA suggests that if segregating U.S. from non-U.S. products is too difficult, then an establishment or company may choose to submit non-U.S. product information to the FDA. While we appreciate FDA's flexibility on the reporting, essentially FDA is proposing that if its reporting requirements are too burdensome or too difficult to comply with, then establishments/companies should provide FDA's jurisdiction, which is a questionable solution.
250	In these instances, if manufacturing process uses the same process and controls data for lots		Further definition is requested as to what is meant by controls data?
253ff	sentence '...with the data from lots imported or intended for import.....'		This part of the sentence is confusing. Should say to just include overall data without any consideration of market/import. Clarification should be given to ensure data meets agency's intent.
261-263	Reporting of data should include all manufacturing operations, including testing, which would be included in a PPR (e.g., lots intended for commercial distribution, post-approval clinical trial lots when the same manufacturing process and controls are used as for commercial lots).		The quality metrics data elements and definitions refer to "saleable units." This is the only reference to "post-approval clinical trial lots". Recommend that clinical trial lots of all kinds are excluded from metrics reporting.

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
265ff	Definition of Lot Acceptance Rate	Please clarify why segregation of lots by saleable, packaging and in-process is important to FDA achieving the stated intent of their program, as it unclear why this level of segregated, and associated burden, is needed.	FDA has changed Lot Acceptance Rate from 2 data elements to 6 data elements to report. The requested data requirements for Lot Acceptance Rate create a more complex approach to calculating LAR and it is not clear how providing more granularity (Started, Released, Rejected for both Saleable and Packaged lots) improves the value. A more common and simplified approach would be to provide data on lots started and released to calculate a LAR for bulk/in-process lots and a LAR for packaged lots. Combining in-process and packaged lots is not current practice. Reporting the number of rejected lots is not necessary for calculating the LAR so eliminating reporting this input would reduce effort.
			There is no provision for a lot that is started in the reporting period but not completed, thus the inverse is also possible. A lot could be completed in a separate reporting period which could result in a rate lower or higher than actual (including over 100%). Line 301 seems to indicate this will be a rare occurrence but in a reporting period with a defined closure date this will be a more common occurrence as lots are more often started and finished on multiple days. Additional information is required for this potential occurrence. There could be a significant burden commenting on for example, lots started in one period but not completed. Clarification should be given to ensure data meets agency's intent.
		Would a business decision (not quality related) e.g. destruction of excess, obsolete or short-dated product be included as a rejection?	The lots would be "rejected", not for failing a product specification, but because there was a business reason for destroying them. We assume these would not be included. Please clarify.
272-273, 281-282	The number of saleable lots, in-process and packaging product lots which were intended for distributed product and were rejected.	Clarification is required please for reporting metric data of partial rejected lots - maybe an example would provide further clarification.	Clarification should be given to ensure data meets agency's intent.
284	Specific criteria for the LAR data	Please provide reference to Appendix where examples are provided	Clarification should be given to ensure data meets agency's intent.
286-288	Examples of saleable lots include bulk tablets, filled vials, bulk milled in-process material if manufacturing is performed at another covered establishment, bulk API, and bulk intermediate API if further manufacturing is performed at another covered establishment.'	Please expand the examples.	It is not clear if an API produced within a firm or by a contract manufacturer transferred to a drug product manufacturing site, meets the definition of a “saleable lot”

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
290--291	A lot may be subdivided or regrouped after the first started lot is initiated. Each subsequent subdivision or grouping is considered a separate lot.	Further clarification is should be given to determine lots that are treated and tested as one lot however are divided into multiple containers. Company practice may not consider these as multiple lots, but sub lots of the original lot.	Clarification should be given to ensure data meets agency's intent.
293	Specific criteria for the LAR data	It is unclear if this also includes in-process lots?	Need clarification and to understand if this include examples of in-process lots
295	(e.g., intended for different countries)	Earlier section 244-259 refers to lots destined for import to the US and implies if lots are designated for other countries than the US they could be excluded. This example adds ambiguity from the previous section by mentioning packaging lots destined for other countries. These could be lots manufactured in the US and destined for other countries.	The Scope should be clarified to discuss metric data from lots manufactured outside US and destined for the US market, and lots manufactured in the US and destined for other countries
298-299	In, general FDA anticipates that the number of lots started minus the sum of lots released and lots rejected will equal the total number of lots pending disposition	Recommend not using this logic to construct lots pending disposition. There are many variables such as the time frame of data pulled, termination of lot due to business (not quality reason) or partial rejections that could mislead and produce false values for lots pending disposition.	Since this is not a correct assumption because lots may be started in one time period and dispositioned in another time period, ISPE continues to recommend total lots dispositioned (lots released or rejected - see ISPE Quality Metrics Pilot Program, Wave 2 Report [1]) as the denominator for LAR.
298-303	We recognize that there are rare instances when this construct will not be valid (e.g., lots pending disposition for an extended period) and we encourage the use of the comment test box to explain the occurrence of such an anomaly.	We recognize that there are ~~rare~~ instances when this construct will not be valid (e.g., lots pending disposition for an extended period)…'	When processing extends across a quarter or year end, i.e. lot is started at end of one quarter, and normal processing and disposition extends into the start of the next quarter, the batch will be in normal work in progress. This will not be a rare occurrence as suggested. Please note that commenting on these normal processing periods which spread across quarters will contribute to the high burden.
301-303		Different manufacturing process have different times for lots pending disposition, what construes an anomaly- how many days pending disposition would be considered an extended period?	Pending disposition may be a normal part of the process.
		Comment box size is a limitation that could prohibit from providing details for each instance, for example comments on multiple data elements	
305	Invalidated OOS Rate Data (IOOSR):	Please provide reference to appendix where examples are provided	Clarification should be given to ensure data meets agency's intent.
305-318	Invalidated OOS Rate Data (IOOSR)	OOS results appear to be requested to be reported separately but they are not used separately in the calculation.	An example where additional reporting contributes to a high burden

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
307-313	The number of lot release test OOS and long-term stability OOS results for the finished drug product or API where the long-term stability test supports the labeled expiration date. The total number of lots release and long-term stability tests conducted for the finished drug product or API where the long-term stability test supports the labeled expiration date.	Please confirm if this would include the reporting of API long term stability tests and OOS for an API manufactured on the drug product manufacturing site - section 348-349 states "A covered establishment that manufactures API used in a covered drug product is not expected to report stability OOS results."	Confirm Scope
		Total number of tests for release and long-term stability are not required for calculating the three metrics. Collecting total number of tests creates additional burden and complexity to the data compilation.	If data is not used for calculation, why are they requested?
		Please clarify that the number of tests equals the number of samples tested or is it the number of tests performed (a test could include multiple samples). The latter would present some additional burden and complexities to acquire.	Clarification should be given to ensure data meets agency's intent.
		Please clarify if “Lot Release Testing" and OOSs are counted for all GMP manufacturing steps including release testing of regulatory starting materials and all intermediates or only included release and stability testing for the final API.	
		Would Tests not required for US release or stability be included?	Confirm Scope
		Add a foot note to clarify that long-term stability tests are any tests on the registered stability protocol.	Clarify the interpretation of the long-term stability tests.
332-334	Then number of total tests is a measurement tool that: (1) provides context for the invalidated OOS rate, and (2) provides a secondary metric for manufacturing performance and ability to produce product within limits (lot release and long-term stability OOS results investigated as a manufacturing aberration divided by the total number of lot release and long-term stability tests performed in the same current reporting period).	Clarification should be given to understand how total tests would provide this detail.	There is burden and complexity to provide this information
		The data submitted would only provide a total number of invalidated OOS due to an aberration of the measurement process and there is not a data point for total invalidated OOS.	Is this what is intended? Consideration should be given to changing the title of the metric
		Recommend not using this logic to determine manufacturing performance. The draft guidance does not request values for manufacturing aberration and calculating this as a value of Total OOS minus 'aberration of the measurement process’ may not be 'aberration of the manufacturing process'. Not all OOS findings can be clearly assigned as a root cause of measurement process or manufacturing process aberration.	Not all total OOS values may not be able to be assigned with a root cause
		Details and calculation for secondary metric should be provided, including if and when this metric would be calculated	Transparency of guidance intent

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
		and used	
320	Specific criteria for the lOOSR data:	This could get confusing for QC lab to report metrics on per product basis, if they run multiple products on one assay run.	Clarification should be given to ensure data meets agency's intent.
339-340	For the purpose of this program, an OOS result should be counted on the day that the test result is completed or the day that an OOS investigation is initiated.	Need to clarify what is meant by the day that the test result is completed (i.e. when the result is first generated or after it has been reviewed and verified for accuracy?)	Clarification to ensure consistency
		Recommend to align date with discovery date of OOS result. Open Investigation dates could fluctuate depending on the event and test result generation may not be synonymous with confirmation that a result is OOS.	Recommend change to definition
345-6	….each test performed ….	More clarification should be provided here that replicate tests are not included as separate tests (e.g. this is made more clear in the Appendix)	Clarification should be given to ensure data meets agency's intent.
348-349	A covered establishment that manufactures API used in a covered drug product is not expected to report stability OOS results	This example does not align with scope suggested in previous sections or examples; if the API manufacturer is doing the stability testing, should they not report the data?	Clarification is need. API manufacturers are requested to have their own products under stability program as per ICH guideline and should have the data.
352	Specific criteria for the lOOSR data:	Clarification should be given if reprocessing stability, validation stability, or lots put on stability due to deviations, should be counted or not	Clarification should be given to ensure data meets agency's intent.
354-355	If a lot release or long-term stability test is conducted multiple times for a lot (e.g., a retest), each test should be counted.	If a lot release or long-term stability test is conducted multiple times for a lot (e.g., a retest) as part of the disposition or stability confirmation decision, each test should be counted.	Only tests performed that are utilized in a disposition decision or to confirm stability should be counted. Re-testing and/or investigational testing may occur during an OOS investigation to identify root cause which would not be appropriate to count.

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
361ff	Product Quality Complaint Rate (PQCR):	There should be text to indicate clearly that PQCR should be reported on a product basis and the Appendices should be constructed accordingly. Please clarify that complaints should not be assigned to an establishment as it confounds establishment reporting vs. FDA's definition	Currently the Appendices seem to indicate that product quality complaints should be allocated to manufacturing establishments, which is extremely difficult to do and in some cases, impossible. While we appreciate FDA's desire to not count a single complaint sent to multiple establishments as multiple complaints, this can be problematic in execution, particularly with establishment reporting. For product-aggregated reporting, when a customer complaint comes into a complaint processing center and is then distributed to multiple sites, which establishment is used for the submission? Is it the customer complaint center, which is not an establishment? Or which of the multiple establishment is it assigned to? For establishment-aggregated reporting, when the complaint processing center assigns the complaint to multiple sites, each site will naturally include said complaint in their establishment reporting, thus multiply count the same complaint. How will an establishment know when to count a complaint as assigned to their establishment, when it has been assigned to many establishments? This difficulty/burden exists solely because of reporting to FDA. For internal purpose, typically companies would query the parent complaint records and count the total and use it to monitor complaints, but because FDA wants the data broken down by establishment, the reporting becomes confounded, overly complicated and inconsistent with how industry tracks it. We recommend complaints not be assigned to an establishment to simplify the reporting.
			Complaints are received many months, sometimes over a year, after the product was distributed. This will lead to a significant time lag between the numerator and the denominator. This will skew the data, particularly for seasonal products or any product/establishment with high demand variability, and may not be an accurate indicator of product quality.
			Under the FDA definition, it seems that complaints for attributes that fall into an acceptable specification limit would be excluded from the count. For example, a broken tablet complaint may fall within the acceptable limits for number of broken tablets so would this be excluded or included as a product quality complaint?

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
			Does the definition include external customer complaints only or does it also include internal, site-to-site complaints? For example, if establishment A sends a complaint to establishment B for the bulk product they just sent them, would this be included as a "product quality complaint". We assume FDA intends it to be external customer complaints only as the stated intent seems to be to use this metric to monitor patient risk. Please clarify.
			FDA's definition of what is a product quality complaint is subject to investigator interpretation, as most anything can be rationalized to be related to quality. There is a concern that fair and reasonable differences in individual perspectives on this may be deemed as a data integrity or as a data error and then result in enforcement action. FDA has implied enforcement action will be used for data collection errors, hence the concern.
			Is a PQC assigned at the point of originated, as classified by the person/group receiving the complaint call (as ISPE's Metrics Definition advised in the Wave 1 and 2 Pilots) or after it has been confirmed (as GPhA proposed)? Please clarify.
		Please clarify whether complaints related to packaging or label damage should be counted as product quality complaints.	We recommend FDA exclude damage to tertiary packaging from being counted and exclude label damage unless the damage covers essential quality information, like lot#, expiry date, etc.)
		Recommend providing reference to Appendix where examples are provided	Clarification should be given to ensure data meets agency's intent.
363	The number of product quality complaints received for the product?	Would this be the total number of opened complaints or just confirmed complaints?	Clarification should be given to ensure data meets agency's intent.
		Clarification is requested for scope of complaints - are only US received complaints in scope?	Confirm Scope. There is some explanation given in Appendix B, lines 768 -772, however, the requirement is not totlally clear.
		Clarify how to report Customer Complaints on combination products/devices used to deliver the product e.g. autoinjectors, prefilled syringes and co-wipes Clarify how units of distribution are defined	Clarification should be given to ensure data meets agency's intent.

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
372-373	'This number does include all potential quality issues, such as subpotency (e.g., a patient report of lack of effect).'	Should unconfirmed all lack of effect claims be included as product quality complaints? The draft guidance states on lines 372-373 that the PQCR number should include "all potency quality issues, such as subpotency (e.g., a patient report of lack of effect)." The example in this statement leaves significant potential for differences in interpretation. Our recommendation is to either 1) remove the example that lack of effect is a product quality complaint or 2) further refine the example that "product quality complaints are when a trend in lack of effect complaints is noted for a given lot suggesting a possible quality issue"	Lack of drug effect can be an inherent part of the drug profile in large number of patients. Reporting occurs through pharmacovigilance/safety reporting.
380 to 381	Reporting establishments may submit a 300-word text comment to provide an explanation of submitted data or report plans for improvement.		Based on what criteria should firms need to develop action plans for metrics? What is the role of FDA related to these action plans? Clarification should be given to ensure data meets agency's intent. FDA does not provide explanation as to what it intends to do with the comment fields. In its 2015 draft guidance, FDA stated that it cannot commit to actually reading the comment fields provided. Is this still the case? Will FDA commit to, not only reading each comment submitted, but also assuring said comments are provided to FDA investigators prior to inspections? Please clarify.
		The 300-word comment field needs to be per site for product reporting and per product for site reporting.	Although we appreciate FDA listening to industry feedback about the July 2015 draft guidance lacking a mechanism to provide comments, a 300-word text field per submission is insufficient to explain data point-specific inclusion and exclusions. Comment location is not clear, for example in Appendix A there is not a column or location for Comments
386ff	How to Submit Comments Within a Quality Metric Data Report and How to Pose Questions to FDA	Comments may include a summary of baseline assumptions the submitter has made during a reporting establishment's review of metric values it has calculated.	A reporting establishment may consider such a comment necessary
399-400	Upon gathering this data, any questions that a covered establishment may have about their specific situation can be sent to OPO-OS-QualityMetrics@fda.hhs.gov.	Please add clarification as to how FDA plans to resolve questions on data inclusions/exclusions and how said resolution will be documented as proof during site inspection.	Is there a specific format for the questions? Is there a turnaround timeline established for FDA response? How are questions processed? This does not appear to be a secure process. Clarification should be given to ensure data meets agency's intent.

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
404-405	To facilitate the quality metrics reporters list as described in section IV.B, a defined reporting period (e.g., a single calendar year) is should be given to reduce discrepancies between site and product reporting.	Is the expectation that a covered establishment will be submitting a combination of site and product reports through specific timeframes.	Clarification should be given to ensure data meets agency's intent.
		It is unclear whether FDA is requesting data submission quarterly or once a year.	Clarification should be given to ensure data meets agency's intent.
404 to 409	How to Report Quality Metrics Data to FDA	Please clarify the due date established by the FDA to submit the metrics? Clarification is required please on when the portal opens in January 2018, specifically what data will be required to be reported (i.e. cumulative quarterly data from Q1-Q3 2017 or 2016 data or current 2018 data. Depending on the product APQR schedule this may differ for each product	Clarification should be given to ensure data meets agency's intent. Reporting data at times other than associated with a product's PPR will add to the burden and have the potential to remove focus by management and staff from assessing and actioning output from PPRs to the task of submitting data to FDA.
408	How to Submit Comments Within a Quality Metric Data Report and How to Pose Questions to FDA	FDA should clarify here that they will not publish confidential information such as the actual metric data	Industry confidence in the agency's intent.
407-409	FDA expects to begin the data analysis when the portal is closed and then publish initial findings and the quality metric reporters list on the FDA Web site.	Clarify when will the portal close in 2018? We recommend it remain open for at least the first 6-9 months as companies will need the time to prepare the submissions.	The guidance states it will be open early 2018 (January) for voluntary submission, but how long do companies have to submit their data? Do companies have until December 2018 to submit their data, or will the portal close sooner than that? Please clarify.
425-426	establish a signal of detection program as one factor in identifying establishments and products that may pose significant risk to consumers	Will the agency be establishing targets and will those be provided to the public? What criteria will the agency use to set the 'signal detection'?	Transparency for industry of FDA criteria and intentions.
427	identify situations in which there may be risk for drug supply distribution	Can examples be provided that demonstrate a link between the data we provide and this conclusion?	ISPE Pilot Program Wave 2 Report indicated that links between proposed FDA metrics with different definitions tested did not show links to supply interruption. To ISPE, risk for supply disruption seems an unrealistic objective using the three metrics proposed. In a recent ISPE Workshop KPIs to monitor drug supply and potential shortages were reviewed and none of the three proposed FDA metrics were included in the list of KPIs.
429	Improve FDA's evaluation of drug manufacturing and control operations	Can the agency provide an example of how they will use the data versus what they see from a GMP perspective (what is the weight of the metrics) - does the FDA intend to provide a rubric for their evaluation?	As an example, will 50% IOOSR rate result in for cause inspection? Can the FDA add further clarification on what is considered an acceptable rate for all three calculated metrics?

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
436-438	FDA intends to use quality metrics, along with other measures, to identify potential shortage signals and engage proactively with manufacturers to mitigate the likelihood of occurrence.	How will FDA 'identify potential shortage signals' from the metric data requested? Can examples of what other measure would be used with metric data to identify potential shortages?	ISPE Pilot Program Wave 2 Report indicated that links between proposed FDA metrics with different but relevant definitions tested did not show links to supply interruption. In a recent ISPE Workshop KPIs to monitor drug supply and potential shortages were reviewed and none of the 3 proposed FDA metrics were included in the list of KPIs. Companies responded that they used a variety of techniques and processes, mostly involving supply chain performance and inventory level monitoring
458ff	FDA intends to publish an analysis of the quality metrics data received on the FDA Web site to share what the Agency has learned from the voluntary phase of the reporting program, and how analyzing these data has affected the frequency of CGMP inspections and the ability of the Agency to address potential drug shortage situations. We also intend to provide opportunities for participating establishments to provide feedback and additional comments, as well as share knowledge from ongoing, industry-driven quality metrics programs.	Please provide written assurance that such an analysis will not contain company proprietary or confidential information as this represents a potential risk to anyone participating in the program.	FDA intends to publish an analysis of the quality metrics data received on the FDA website to share what the Agency has learned. We recognize FDA's good intentions with being transparent about the benefits and challenges experienced during the voluntary phase and giving visibility to the how this affect inspections. Please provide written assurance that such an analysis will not contain company proprietary or confidential information as this represent a potential risk to anyone participating in the program. When is the FDA intending to publish this? Will this publishing include identifying information? Will establishment metrics or actions plans be published in this analysis?
		Please clarify what "participating establishments mean". Does "participating" mean only those companies that qualify to be on the Reporters List, or is it anyone that voluntarily submits data to the FDA?	It is unclear what "participating" means exactly, given that there are multiple ways to participate. For example, if a company voluntarily submits its data, but said submission does not qualify to be on the Reporters List, is this still considered participating?

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
465	Quality Metrics Reporters List	It is suggested that such lists are not published in order to maximize participation in the program.	The reporters list recognition categories: a) Add complexity to the voluntary program: b) May be misinterpreted as an evaluation of quality performance and used inappropriately. All parties in purchasing chains are responsible to assure quality of their supply chain partners regardless of list. c) May penalize firms who may not have legal access to the data or ability to divert/assign resources to collect and submit to agency, hence compromising their reporting tier level FDA believes there is benefit to publicly sharing the names of establishments that voluntarily choose to submit quality data to the FDA, because it demonstrates a willingness to proactively engage with the Agency in pursuit of the goals described in its guidance. Unfortunately, following the revised guidance, a company can be very proactively engaging with the agency, have great intentions and passion for quality and still not be able to get on Reporters List, by virtue of how FDA has designed it. A company's ability to get on the list has nothing to do with their product quality or willingness to proactively engage. It has everything to do with how readily they can access data from all their API suppliers, CMOs and establishments in the way FDA has defined the data. By its very nature, the Reporters List will have the benefit of showing who has the simplest supply chain, fewest number of products and sites to report; not who is willing to proactively engage. For example, if a company has 1 CMO or API supplier who refuses to report data, or, 1 establishment who for 1 product cannot produce 1 data element as FDA has defined it, then the company cannot get on the list, regardless of how transparent, willing and committed to improving quality monitoring.
465	Quality Metrics Reporter List	There are no criteria identified for if, when or how a reporter class would change. Is it an isolated event based on most recent report or a holistic approach? For example, on a quarterly basis a reporter could meet different categories. Would they receive the most recent designation or an aggregate or the lowest based on least common data provided?	Clarification should be given to ensure data meets agency's intent.

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
467ff	How FDA Intends to Use Quality Metrics	CMOs may have incentive to publish their own metrics and submit site reports, and hence may not want to give customers product specific metrics. It is considered by some sponsors more work for the CMO to segregate metrics per product, easier for them to just consolidate into one overall site report.	Some sponsors consider a CMO may wish to publicize their complete performance (e.g. as a Site Reporter Top Tier) rather than have their performance emerge from an FDA analysis across different products and covered reporting establishments. Clarification should be given to ensure data meets agency's intent.
477	This list may be useful to establishments within the pharmaceutical manufacturing industry when selecting contract manufacturers and component suppliers….	Current metric data does not appear to provide data indicating component suppliers?	
		How will covered establishments (e.g. CMOs) that are incorporated into product reporting establishment be recognized?	
482-484	The list will provide information about whether an establishment voluntarily submitted quality metrics data to the Agency, and if so how much data was submitted.	The list will provide information about whether an establishment voluntarily submitted sufficient quality metrics data to the Agency, exactly as the Agency has specified, to qualify to be listed as a reporter	FDA's statement should be modified. The Reporters List will provide names of establishments able to meet exactly FDA's definitions for the 11 data elements requested for 100% of its entire supply chain and be able to incur the significant financial burden to do so and be willing to take the risks associated with submitting voluntarily data to FDA on a program that has still to be tested. There are valid reasons why a company would choose not to participant in this early phase of the program that are well beyond their willingness to engage or be transparent. Data submitters that have any gaps in their data or that simply find the way FDA has defined its reporting to be difficult for them to achieve may not appear on the list at all.
485	Quality Metric Reporters List	Please clarify that confidential data, actual metrics etc. will not be made public	Industry is extremely concerned regarding inappropriate publication and use of data which it considers confidential and business sensitive

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
487-505	The Agency will identify participating establishments of the FDA Website according to the following recognition categories……	It is recommended that public reporting is removed from this guidance.	The Reporters Lists are related to ability to report completely, not the quality or difficulty of these reports, or of more concern, the Lists have no relationship to quality performance. They may mislead and consequently act as a disincentive for companies to participate in the voluntary phase of the program. Categories do not provide context to covered establishments participation. For example, a company with 100 products that submits 99 would be categorized the same as a company with 2 products and only submitting one. Additionally, a company submitting 99 out of 100 product metrics would be categorized the same as a company submitting 1 out of 100 product metrics. Similarly, an establishment with 1 product and simple supply chain could be a Product Reporter Top Tier even though the actual metric values were not themselves 'good'. The guidance is considered to be biased towards companies with simple supply chains and few products and against drug manufacturers with a high number of products and complex supply chains. There is not a relationship to quality performance. FDA, by publishing its "Tier" list, will put companies in the position of sharing their private data publicly. Once the list is published, purchasers, suppliers and healthcare providers may insist on seeing a company's quality metrics data submitted to the FDA as part of continuing business. FDA, by its actions, may create liability for companies in such situations, without any gain for the company or public health. How does the agency plan to verify the submitted data to ensure completeness?
490-517	Product reporting vs site reporting		How does the agency plan to differentiate between a global company and specific manufacturing site owned by that company?

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
490	API reporter		It is still unclear when contract API manufacturers need to or should report their data. Since only drug products can be marketed, then it would seem like API data could be incorporated into a drug product report. If an API manufacture wants to submit a site based report, should they include all data for all products or just those for which data was not already submitted to the license holder, or indeed another site e.g. CLO, for inclusion in a drug product report, or just the data generated at the API manufacturing site? For such APIs, how should this be reported? Again, examples of this would be most helpful.
507-517	For site reporting establishments	Will a covered establishment that reports through product reporting and not site reporting be given a poor categorization under site reporting or vice versa?	It will be hard or even impossible for FDA to know for a site the proportion of products reported.
521-527	If product reporting establishments Company ABC submitted a report identifying all establishments in the manufacturing supply chain for all covered drug products (or APIs used in the manufacturing of a covered drug product), and metrics data was provided from the primary manufacturing establishments....	Please clarify the difference between 'primary manufacturing establishment' and 'other establishment' in the manufacturing supply chain.	Additional information should be given to understand priority of data compilation.
		CMOs may wish to report product data in their site report, rather than give to customer for their product report	Provision of quality metric data will give increased complexity in working relationships between CMOs and clients and may lead to some tension.
541-544	FDA does not intend to publicly disclose information submitted to the Agency as part of the voluntary phase of the quality metrics program that is exempt from disclosure under the Freedom of Information Act as confidential commercial information, e.g., information that would reveal nonpublic commercial relationships and production volumes.	FDA needs to provide stronger assurances than what is stated here.	Industry has concerns regarding public disclosure of quality metric data and information, and consequent misinterpretation, either from FIO requests or through hacking. Assurance is required that data submitted on a voluntary basis will have protection against sharing with the public and other agencies.
541-542	..as part of the voluntary phase..		There is an inference that FDA may publish information in a subsequent non-voluntary phase. It is considered that FDA should not publish confidential quality metric data - industry has concerns regarding publication of data it considers confidential and potential misunderstanding of these data
543 - 544	…reveal nonpublic commercial relationships and production volumes.		Even if a commercial relationship is public information, FDA should not reveal this; We recommend that this relationship be kept confidential and not shared publicly. Clarification should be given to ensure data meets agency's intent.

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
545	Glossary	Please add definitions for Saleable unit, In process and packaging product lots, Application product, non-application product	Clarification should be given to ensure data meets agency's intent.
592-596	Accepted Lot – a started lot which has been released for distribution or for the next stage of processing. If the lot is released with an unexpectedly low yield due to an assignable out cause and the associated investigation supports the release of the lot, it should be considered an accepted lot. Investigations into low yield results should be thorough and managed by the quality unit.	Follow up sentences are more examples than definitions that potentially increases ambiguity and not relevant to this definition.	These sentences would be better suited in an example section and not part of the definition?
596-598	If a lot number is closed, the lot is transferred to a new lot number, and subsequently released, only the original lot should be counted. An accepted lot should be counted on the day of the final disposition decision.	Some manufacturing practices may not align with this theoretical example as the newly assigned number is then tracked through the process. Only the original lot number would be used to identify lot started and not the acceptance of the lot.	Provision should be added to accommodate differences in manufacturing processes, but agree with this example one started and one accepted.
598-603	It may be possible that an accepted lot is no longer considered accepted (e.g., a stability failure, a quality problem identified by a contract packager, or in the marketplace). In this case, the lot should no longer be counted as an accepted lot. If the change in disposition decision is after submission of quality data, the reporter may submit an amendment and it would be helpful if the amendment is available for discussion during a future on-site inspection.	What is the statute of limitations for an amendment? From a product report perspective data could be live which could result in potential changes after the submission. Will Product report submissions be the subject of on-site inspections? What are the consequences for identifying changes in the submitted data? As a product reporting company or site reporter at the time of the submission the data will be accurate however following the submission confirmation of data may be required as the data is active and in real time.	Clarification should be given please
607-610	If the manufacturing spans multiple time segments (quarters), the started lot should be counted when the lot number is issued or the API or primary starting material is physically charged.	This is an example of where a lot acceptance rate could be misaligned due manufacture spanning multiple time periods not due to a quality related issue.	
612-613	Reference 46 For example: (1) if the power fails halfway through a tableting operation and a portion of the manufactured tablets are acceptable to release for distribution, this is considered an accepted lot,	This could also be considered a partial rejection - how will this situation be reported?	

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
613-615 and footnote 28	Lot Release Test – includes all tests of conformance to final specifications, including all real-time release tests, and all in-process tests that act as a surrogate for final lot release (e.g., real time release testing is approved in the application). Footnote 28 - Reference this guidance's Glossary for OOS result (e.g., lot release tests and long-term stability tests only). A single result (e.g., one value on a Certificate of Analysis) may result in only one OOS test result.	Revise definition to include implication of foot note 28. For example, the number of release tests will equal the number of individual results reported on the CoA. For example, one HPLC Assay maybe be run but the CoA may include purity, assay (w/w%), Impurity 1 (a/a%), Impurity 2 (a/a%), Impurity 3 (a/a%), Impurity 4 (a/a%), any unidentified impurity >0.1%, and total impurities. Thus, one HPLC test provides 8 potential OOS test results and thus counts as 8 release tests.	The definition of Lot release tests does not fully align with footnote 28. We have suggested some additional text to help clarify the intent.
614 and 621	< definition of OOS Result>	Please remove "surrogate for batch release" from the OOS Result definition and provide more clarity on which in-process tests to include and exclude.	FDA excludes in-process testing, environmental testing, raw material and packaging component testing from reporting. However, on page 18, lines 613-615, and in its Webinar, FDA includes these if they act as a surrogate for final lot release. The inclusion of "act as a surrogate for lot release" adds unnecessary complication to this metric. It is much less burdensome and more standard if the definition on page 10, lines 357ff is followed, that is, do not include "act as a surrogate for lot release", as it is nebulous and highly open to individual interpretation. For example, whether or not an in-process test acts as a surrogate for lot release may not be clear. An in-process test may not appear on the final FDF release specification; however, a batch record reviewer may look back at an in-process test and find something that makes them not want to release a batch. What is the value of adding "surrogate for batch release" as a proviso to the definition vs. what FDA would lose information-wise vs. impact to FDA's stated goals of the program? It adds complication but seems to add little additional value so recommend it be removed from the definition.
626	aberration of the measurement process	Further definition is requested of 'aberration of the measurement process' and to include examples to better understand scope. For example, not all OOSs may be allocated to a specific root cause such as manufacturing OOS or analytical OOS. Are such non-assigned OOSs, which could be considered Invalidated OOS values, assigned to the 'aberration of the measurement process' category?	Clarification should be given to ensure data meets agency's intent.

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
644-646	Product Quality Complaint – a complaint involving any possible, including actual, failure of a drug to meet any of its specifications designed to ensure that any drug conforms to appropriate standards of identity strength, quality, and purity.	Further clarification if scope is for confirmed complaints only or all reported complaints?	The definition of product quality complaint needs to be clarified (see comment for line 222 above)
647-678	Page numbers 17, 18, and 19	Page numbers 17, 18, and 19 are duplicated and already exist in the three prior pages	
674ff	Appendices		It is still unclear how reporting by product is supposed to be reported. Again, examples would help here. Is it the expectation that one file for each product (using for example Appendix A-1) would be submitted and that a new row would be created for each site/entity in the supply chain starting with the API manufacturer and including all testing and packaging sites? Each site/row would then have its own set or likely subset for metrics. It is unclear how these can be added together or rolled up to provide one overall set of metrics for that one single product. How does one avoid duplicate counting of OOS, and complaints. API manufacturers typically measure complaints per kg or 50kg units (see below) and drug product manufactures measure complaints per pack. How are these to be combined? Again incorporating detailed and complex example submission forms that address these common but complex scenarios would be great helpful.
647ff	Appendix A	In the detailed appendices, there are columns to enter the raw data, but not for the calculated final percentages. It is recommended columns should be added so firms can provide not just raw data, but final calculated data	Clarification should be given to ensure data meets agency's intent.
672	Appendix A	Clarification is requested regarding how reports are completed when a manufacturer or CMO has partial testing responsibilities and another CMO/CLO may perform other tests.	Clarification should be given to ensure data meets agency's intent.
Appendix	Supply Chain/Process Stage Code	Clarify the meaning and source for this code	No guidance is currently provided in the draft metrics guidance or technical conformance guide
	Appendix	The appendices indicate the sum of release and stability results are to be reported, however it is not clear in the body (305-319) that the sum is reported.	Please add text in IOOSR section to clarify

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673-684	Appendix for Product Review	What happens if there are two manufacturing sites for the drug product and they are both owned by the drug product reporting company? (no CMO involvement)? What happens if there is one manufacturing site for the drug product and they as well another establishment share lab responsibilities? What happens if there is a primary manufacturing site is owned by product reporting company however there is a second or back-up establishment (CMO) for business continuity. They both perform the same operation.	Please indicate how product reports are completed. Clarification should be given to ensure data meets agency's intent.
Pages 7, 9 and Appendix B			The order in which PQCR and IOOSR appear in the text is reversed on page 9 compared to page 7 and Appendix B. Please rearrange order for consistency and to remove confusion for the reader.
720	Appendix B	More specific examples are requested please, where they provide example data values, show the equation used, and calculate the final metric value. It would be very helpful to have an API example, an unlabeled DP example, a packaged lot example. It would also be very helpful to have examples where FDA uses data elements not used in calculation of metrics.	Such examples will help reporters to understand how metrics are calculated and other data elements are used by FDA. Clarification should be given to ensure data meets agency's intent.
734 - 740	For an OTC monograph product, one batch of saleable product is packaged into an unlabeled primary pack and the primary pack is subsequently labeled and placed into secondary packaging at three different packagers. In this scenario, all four of these facilities are considered covered establishments (one for the bulk manufacturing and three for primary labeling). For the manufacturer of the unlabeled primary pack OTC product, the unlabeled primary pack lots are saleable lots. The lots which are distributed by each packaging establishment are also saleable lots.	For an OTC monograph product, one batch of saleable product is packaged into an unlabeled primary pack and the primary pack is subsequently labeled and placed into secondary packaging at three different packagers. In this scenario, all four of these facilities are considered covered establishments (one for the bulk manufacturing and three for primary labeling). For the manufacturer of the unlabeled primary pack OTC product, the unlabeled primary pack lots are saleable lots. The lots which are distributed by each packaging establishment are packaged lots.	In this example, when the unlabeled primary packages are labeled and packaged into secondary packaging at the three different packagers, each of these lots should be considered packaged lots based on the prior definitions.

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
742 - 748	Facility A manufactures the product and Facility B packages the product. Facility B discovers a defect that leads to the rejection of the lot; the defect was due to the manufacturing at Facility A. In this situation, Facility A should not count this product lot as a released lot, despite the initial release. For Facility B, if the defect was discovered upon incoming acceptance testing and the packaging lot was not yet started, the lot should not be counted. If a packaging lot was started, it should be counted as a lot started, not as a released lot.		Comment 1 In this example, should the manufacturing site (Facility A) count the lot as rejected, albeit retrospectively? And how should the packaging site (Facility B) count the disposition of the packaging lot? Should Facility B count the lot as rejected? Comment 2 What happens at Facility B and Facility A if the packaging was started and the defect was determined at release testing at Facility B? Would both facilities count the lot as a rejection?
			Changing the release status at Facility A once the product has been released to rejected may not align with industry practices. Lot reject would still occur but may be documented in different manner e.g. documented only at Facility B.
750-752	the count of lots depends on whether the separate pan loads are considered unique lots or if the loads are part of a single started lot.		None of the LAR examples mention that the count of the lots depends on whether there will be a disposition decision associated with the lots. For example, see lines 750-752.
755-758	Facility A initiates manufacturing of Product Z in the last quarter of the reporting cycle or ceases manufacturing of Product Y in the first quarter of the reporting cycle. An explanation of the partial year can be described in the comment field. The product report or site report would be considered complete for that product.	Industry expects that this would a common expectation at the end of every reporting cycle for every product. Providing comments for each instance may become an overwhelming burden.	
759	Product Quality Complaint Rate - Examples	It would be helpful to include an example when a complaint involves both an adverse event (e.g., rash on face after using face cream) and a product quality complaint (the product had an off odor) - should this be reported as two product quality complaints or one for FDA Quality Metrics?	This situation occurs infrequently but regularly for OTC products where the consumer may truly have two quality issues, one issue that causes both an observable product defect and a reaction after use or they are trying to support their complaint with additional "evidence" to help ensure they receive a refund or incentive
763-766	If a lot is distributed and a single customer submits the same complaint from different departments, only a single complaint should be counted. If submitting a site report, the covered establishment may choose to include this complaint in their data if it is the least burdensome option.	Provide example or details where we would not include a complaint in our submission for site.	

Line Number	Current Text	Proposed Change or Comment	Rationale or Comment
774-776	For a site report by a packager, if a complaint is received and potentially due to the packager's operations (e.g., discolored tablet or powder), the complaint should be counted by the site reporting establishment.	Please clarify if this is just US complaints?	
FRN	Voluntary phase is targeted for Early 2018 (January 2018)	Please clarify expectation of data to be reported in 2018, will this be 2017 for one calendar year or a smaller subset, or 'live' 2018 data?	The industry is anxious to participate in the voluntary phase of the metrics however the proposed timeline would require the industry to have systems in place to ensure all components can begin being captured at the start of January 2017. Due to the complexity of setting up quality systems and compiling this data additional time may be warranted to ensure the industry can participate to its fullest intent in the voluntary phase.
		Opening of portal for submission is proposed as January 2018 - how long will the portal be open to allow companies to submit data?	Information required to help companies decide if they can be ready to participate
Webinar - Slide 24	Since this is a contracting site, those lots that I just described are considered saleable.	The three lots in this example were packaged product, therefore, it would be more clear to report these as packaged lots rather than saleable lots.	It is unclear why a contracting situation would change the application of "saleable" and "packaged" lots which will lead to confusion without greater clarity on why the difference