September 23, 2016

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

Attention**: Docket Number: FDA-2016-D-1594** "Quality Metrics Technical Conformance Guide—Technical Specifications Document."

Dear Sir or Madam:

ISPE (International Society for Pharmaceutical Engineering) would like to submit comments for the FDA draft Quality Metrics Technical Conformance Guide—Technical Specifications Document. The following pages contain both general and specifc comments on the document.

ISPE appreciates the opportunity to submit these comments for your consideration.

Sincerely,

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Comments on Docket No. FDA-2016-D-1594 for "Quality Metrics Technical Conformance Guide—Technical Specifications Document."

Comments submitted by: ISPE (International Society for Pharmaceutical Engineering)
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OVERVIEW	ISPE understands and appreciates that FDA is anticipating issuance of the "Submission of Quality Metrics" in 2016, which will be a revision to the previous draft guidance "Request for Quality Metrics" issued in July 2015. Consequently, ISPE has limited its comments to those that are directly related to the Technical Conformance Guide. ISPE understands that the Request for Quality Metrics draft guidance is the "what" relating to submission of quality metrics data to the FDA and the Quality Metrics Technical Conformance Guide is the "how" to submit data points electronically. Within this context, ISPE considers that additional detail and clarity in the Technical Conformance Guide would be beneficial in areas such as technical specifications, definitions and format for submission of data in XML, as described below.

GUIDE SECTION	COMMENT(S) AND ANY RECOMMENDED ALTERNATIVE TEXT	RATIONALE Where appropriate
HIGH LEVEL COMMENTS AND COMMENTS GENERAL TO THE WHOLE GUIDE	**Burden** Clarification is requested regarding the level of reporting drug product data points. If reporting at the NDC level is required, it will be burdensome and the burden is projected to be higher than that estimated in ISPE Wave 2 Pilot Report[1]. Additionally, reporting at the NDC level could be extremely complex since some quality metrics data points (e.g. OOS at a bulk product stage) may occur in a	ISPE is concerned about the burden for the following reason: The high burden estimates from ISPE Pilot Program, Wave 2[1] are based on aggregation to product application level with strengths and packs grouped together for Rx and Gx and **not** to the NDC level, which requires more data points. Following is a summary of burden considerations based on Design and Data from ISPE Wave 2 Report[1]: • The ISPE estimates, which are 3 times the FRN estimates are based on: o Self-selected sample mostly with single manufacturing site (c.f. FDA assumption of 5 to 10 sites) o Sample mostly with mature systems o Collection of 8 data points in Pilot rather than 10 in the Guidance • The ISPE estimate could be **LOW** because:

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	process before the NDC code is known. Allocation of such a data point to an NDC code could be difficult and may occur in a different reporting period i.e. quarter.	o It is based on aggregation to product application level with strengths and packs grouped together for Rx and Gx. The estimate could be HIGHER if data are required at NDC level of strength, pack, and count level for four periods in a reporting year. The Guide seems to request data points at the NDC level (see response to sections 4.2.1, 4.2.6 and 4.2.10) o OTC sites required 60% more effort to collect data and they aggregated to 'similar product range' level. Hence burden for OTC products could be even HIGHER than ISPE estimate o An industry-wide sample is likely: – To have more sites and complexity in the supply chain – To include more use of CMOs – To have less mature with more manual collection systems Potential suggested solutions were given in ISPE's response[2] to the FDA draft guidance and are summarized as: • Start with a small, targeted approach • Use a phased introduction, for example starting with a voluntary program • Start with 3 of the proposed metrics using definitions suggested by ISPE and using more site-based reporting: o Lot Acceptance Rate on a **site-by-product** basis o Product Quality Complaint Rate on a product basis o Invalidated OOS Rate on a **site-only** basis • Defer some metrics and data points
	Definitions 1. The definition of 'drug product' for this Guide needs further clarification as it may lead to different interpretations: a group of products of the same formula, one formula, one strength, one strength in one pack, one strength in one pack size?	ISPE experiences with Wave 1[3] and Wave 2[1] Pilot Programs have affirmed that clear, consistent and specific definitions are extremely important to a harmonized quality metrics program. Definitions are critical to the success of this program for FDA and for industry.

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	The same drug product which is both Rx and OTC (or Gx) is the same or different? 2. Further clarification is requested about the way that metrics are calculated from the data requested in the Guide; for example is the metric calculated at the product application level or at the NDC level? Including example(s) for each metric will be valuable in ensuring consistent interpretation and reporting 3. It would be beneficial if the Guide has clear definitions linked to the Guidance (Appendix A) 4. The Guide needs to state clearly that data points are required per 'drug product', per quarter on an annual basis. (Quarterly reporting contributes to the high burden compared with annual reporting as recommended by ISPE [2]).	To assist with clarity and provide correlation and transparency between this Technical Conformance Document and the FDA Draft Quality Metrics Guidance. In ISPE's response to the FDA draft guidance[2] it was recommended that submission of data points should be on an annual basis rather than quarterly to reduce the burden on industry.
	Data Submission and Validation 1. Careful consideration needs to be given to security aspects of using a data system, which facilitates *"…the sharing of structured data across different information formats"* (XML). 2. We recommend that data validation rules be published for public comment before implementation 3. We believe that substantially more	For example there could be unintended consequences of sharing such data with e.g. Other departments, agencies etc.

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	detail is needed regarding the process of submission of data e.g.: • More technical specifications, definitions and format are required for submission of data in XML e.g. number precision, date formats, standardized wording/allowed values for "text" fields, etc. Where helpful, explanation of how to submit fractions for partial dispositions, XML format structure is requested. • The submission process of the quality metrics data would be enhanced if FDA could provide the option of using CDER Direct to submit the quality metrics data. This would also reduce the burden and would provide companies with two alternative ways of submitting data.	A company experience and suggestion is given in response to section 2.1 below.
	Other Comments 1. The Guide suggests alternative approaches can be used, however, we are not aware of a practical way to use an alternative approach. 2. The Guide does not provide for comments to explain data – this was a key point of industry feedback to the Guidance and fits with the FDA objective in the Guide of a *"….quality*	This guidance contains very structured data reporting expectations thereby appearing to preclude the stated option of using alternative approaches. Possible solutions include providing more flexibility with reporting options such as CDER Direct or provision of metrics being reported formally using other tools. Industry feedback during the draft guidance comment period was strongly in support of the need for providing the means to submit comments with the data. A solution is for FDA to specify in this guide the mechanism for providing notes or comments on individual data points in order to put the data in the proper context.

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	metrics program can be best achieved through collaboration and a shared understanding of standards for metric indicators and data exchange/reporting"	
	3. It is recommended that FDA establishes some form of 'helpdesk' to provide support to companies during the implementation phase. Additionally ISPE strongly recommends that FDA provide formal training oportunities for industry e.g. webinars, workshops, e-learning to ensure consistent interpretation within and across both FDA and industry over time	Both Wave 1 and Wave 2 Pilot Programs[1,3] demonstrated the important and essential role of a "helpdesk support" in helping companies set up their collection and reporting systems. McKinsey and Company, a third party that collected data from the participating companies, provided this support for the pilots. They also provided ongoing support to participants by clarifying data points in relation to definitions and assisting companies to 'clean up' their data to make them consistent prior to submission. The recommendation to provide formal training environs in addition to the acute support provided by a Help Desk is to ensure consistent interpretation within and across both FDA and industry over time
	4. More clarification is requested regarding submission of API data e.g. • API manufacturers do not know and cannot easily access which drug products their APIs are used in e.g. section 4.2.1 • Scope of API, namely if it includes i) registered intermediates; ii) the entire synthesis process or iii) just from final crystallization onwards or even iv) just from the physical handlings for products with sieving/milling should be provided. This clarification will provide industry with a better sense of the burden given to the	

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	organizations. • Does 'drug' in the Guide mean FDF and/or API. Should it be referenced 'FDF/API'? 5. The use of the word 'establishments' needs further clarification throughout the document.	Footnote reference 4 to section 4.2.13 says "In this section of the guidance, "establishment" means "covered establishment" as defined in the FDA guidance for industry on *Request for Quality Metrics*." Does this refer to section 4 or section 4.2? In section 5, page 13, third line from the bottom, it is not clear which type of "Establishments' (covered, reporting or both) is referred to.
TABLE OF CONTENTS	Table of contents is missing 4.2.12, 4.2.15, 4.4 and 4.4.2	Typographical error - needs be noted and corrected
1 INTRODUCTION		
1.1 Background	It is stated: "…this technical reference document continues FDA's policy efforts to ensure successful implementation of CDER's objectives outlined in the 21st Century publication." However, based on ISPE's Wave 2[1] pilot findings on industry burden, we are concerned that the feasibility of FDA achieving said objectives via the quality metrics program may be jeopardized by the high burden it will impose on companies.	ISPE is concerned that the burden associated with this program may be high as shown in the ISPE Wave 2 report[1] and the high burden is likely to impede FDA in achieving what it intends. Options for reducing the burden on industry include voluntary deployment, starting small, use a phased approach and change metric definitions to be more feasible to collect and of greater value as indicators of quality. The anticipated burden may impede companies' ability to invest funds and resources in state of the art technologies and early adoption of advances and enhanced quality system approaches.
1.2 Purpose		
1.3 Document Revision and Control		
1.4 Relationship to		

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Other Documents		
2 EXCHANGE FORMAT – ELECTRONIC SUBMISSIONS		
2.1 File Transport Format	Electronic submission standardization if using XML is recommended. More detail regarding the process of submission of data is requested, e.g. • More technical specifications, definitions and format are required for submission of data in XML e.g. number precision, date formats, standardized wording/allowed values for "text" fields, etc. Where helpful, explanation of how to submit fractions for partial dispositions, XML format structure is necessary for clarity The submission process of the quality metrics data would be enhanced if FDA could provide the option of using CDER Direct to submit the quality metrics data. This would also reduce the burden and would provide companies with two alternative ways of submitting data.	A company experience is: "The FDA Quality Metrics draft guidance requests that all quality metrics data reports are to be submitted through the FDA Electronic Submission Gateway (ESG). FDA does not envisage that there will be any additional burden associated with using the ESG, because reporting establishments are already required to use the ESG for FDA establishment registration & drug listing. However, some companies do not have the resources and expertise to create the required Extensible Markup Language (XML) files in the Structured Product Labeling (SPL) format for submission directly through the ESG. Firms currently have to pay consultants to submit data on their behalf. Additional reporting of quality metrics through the ESG will therefore result in an extra financial burden.

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		In September 2014, FDA launched a free, alternative on-line tool that allows pharmaceutical firms to create, review, save, and submit certain SPL files through the ESG without the need of the Web Trader account and digital certificates that are required for direct submissions through the ESG. This new system (CDER Direct) features a form-like data entry interface and provides tutorial slides, descriptive text, helpful links, and submission status. CDER Direct currently allows submission of establishment registration, drug listing, GDUFA self-identification, NDC/NHRIC Labeler code requests and Wholesale Drug Distributors & Third Part Logistics Facility Reports. The submission process of the quality metrics data would be enhanced if FDA could provide the option of using CDER Direct to submit the quality metrics data."
	Some concerns: What is the security on the proposed file structure? What assurance is there that if the data from a XML file is required for use in statistical software that it will transfer over correctly?	If FDA will be using a package such as JMP, SAS, R, SPSS, Minitab, then the software and data transfer process need be vetted to ensure that the XML files can be read in these software After data transfer processes have been verified a notification to industry that data transfer does not lead to corruption, would alleviate any concerns
2.1.1 Extensible Mark-up Language	Last sentence here reads "XML's primary purpose is to facilitate the sharing of structured data across different information systems." It is not clear if the above statement means that data will be shared across different systems within the FDA or outside of the FDA easily. Assurance that this data is not used for purposes that it was not intended for, would be appreciated.	ISPE recognizes that FDA has procedures for receiving and handling data provided in XML format and that some experts in industry and FDA are familiar with the relevant processes. Provision of quality metrics data, however, is likely to involve a wider group of experts in both industry and FDA, many new to the process of electronic submission. For the benefit of this wider group, consideration need be given to security when submitting and further processing data. There is at least one case where information considered proprietary by a company in an NDA application appeared in public via correspondence from another FDA department. A comment on the Data Security would be appreciated.
3 FILE FORMAT –		

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ELECTRONIC SUBMISSIONS		
3.1 Variable and Dataset Descriptor Length	Is “Variable Name” the same as “Data Element Name”? If so, then data elements “DOSAGEFORMS” and “APRAPPVDY” exceeds the 8-character maximum shown in Table 1.	This needs correction / clarification in the guide
3.2 Special Characters: Variables and Datasets		
3.3 Variable and Dataset Names		
3.4 Variable and Dataset Labels		
3.5 Data Definition File		
4 GENERAL CONTENT AND FORMAT OF A SUBMISSION	It is recognized that having all data points provided at the same time and consistently to an interface is helpful to FDA. However, some of the data being requested are already reported to the FDA through regular order of business, such as annual reports and submissions. Ideally, establishments should not have to supply information that the FDA already receives from them or their companies	Requiring companies to submit data they have already supplied to the Agency could contribute to the burden. A solution would be to remove data submission requirements for any data already submitted to the Agency.

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4.1 Data Element Specifications	FDA's draft guidance also specifies reporting of the Total Number of Products Produced at the Establishment during the reporting period. This is the denominator for the APR/PQRs Completed Within 30 Days metrics. It is not mentioned nor described in the Technical conformance guide. FDA did not count this as a data point in its draft guidance either, stating that they required 10 data points to be collected. It is actually 11 with this data point.	The Technical conformance guide needs to address all data points FDA is requiring establishments to submit per its draft guidance and "Total Number of Products Produced" is not listed. The solution is that FDA supplies the definition for this and the XML data type, or be explicit that FDA will calculate this point from the data feed themselves. This requires clarification in both the draft guidance and the Technical Conformance guide.
4.2 Data Elements - Descriptions		
4.2.1 Drug Product Name	The site/establishment given in a license may be a contractor	Does Sponsor enter the requested data in this situation or the CMO site? ISPE recommended in its response to the draft Guidance[2] that quality metrics data are submitted using more site-based reporting to reduce burden and be more in alignment with current practices employed by much of industry. Clarification is requested for this point.
	What is the definition of a drug product for the purposes of this guide – one formula, one strength, one strength in each pack type or pack size? Please also refer to comments regarding NDC product code, section 4.2.10.	Clarification is requested regarding the definition of drug product for this Guide.
	In cases where API manufacturer is the holder of the DMF, the manufacturer does not know the drug product where their API is used in. The guide needs	API manufacturers supply many pharmaceutical companies. The same API is used in many different FDF/Drug product names and is not possible for the API manufacturer to provide all of them. It is not practical as mentioned in the comments related with the draft FDA guidance for industry on *Request for Quality Metrics"*[2] for API manufacturers

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	clarify that the API/Drug substance name provided is the name indicated in the API manufacturer DMF. It is also recommended that the scope for API's be clearly stated (does it include registered intermediates? what is considered API? from final crystallization or if milled/sieved only from the physical handlings?)	to provide the data to each of their FDF customers.
4.2.2 Drug Designation	Products can be both Rx (and Gx) and OTC, particularly if different strengths exist. Is this data element restricted to two options like “Drug Product Type”? By restricting the Drug Designation to one or the other and not both, it implies that the Quality Metrics have to be submitted not only by product but also by strength. Section 4.3 needs be aligned to add N/A to reflect section.	If a product is both Rx and OTC based on different strengths, then restricting it to one or the other will be extremely difficult for reporting. Clarification is required as to whether establishments are to report data by strength and product and not by product type where a drug has multiple designations. Element is not required to be reported for an API intended for use in the manufacture of a drug product.
4.2.3 Applicable Monograph	ISPE is requesting clarification as to why submission of ‘Applicable Monograph’ is helpful to understanding quality metrics data. Clarification is requested if only USP or also if other monographs like EP are allowed	ISPE is not clear of the rationale for requesting Applicable Monograph. If required, this information may be available from other sources, for example NDC number. Additional burden is placed on establishments when information to be gathered, reviewed and reported may be already available, e.g. via NDC and may not be used directly evaluating quality metrics data. Clarification is required as some products/APIs are analysed according other pharmacopoeias and not only USP.
4.2.4 Drug Product	If API also means regulated intermediates, some are used in more	Clarification is requested

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Type	than one API. This possibility needs be considered. If a drug product will also be used as part of a combination product, what "Type" should be selected?	
4.2.5 Applicant Name		
4.2.6 Final Labeler Name	This has to be entered per dosage form. Not applicable to API manufacturers Can this information be extracted from the NDC Number?	It is not uncommon to have multiple partners used in final labelling. In section 4.3, it is unclear whether the system will accept multiple entries for each labeler OR if the applicant needs to enter a data set for each NDC code. It is also unclear whether FDA is proposing to calculate metric data points at the labeler level or at the drug product level and the labeler name will be used in some other way. An example calculation will help clarifying this point. If the calculation is at the labeler level then the impact on the burden is significant and this was not estimated as part of ISPE's Wave 2 Pilot[1].
4.2.7 Final Labeler Codes	The description asks for name of the labeler for validation of the text entered as "final labeler name". However, the title of this data element is 4.2.7 Final Labeler Codes. Unlike the label name that is a text, label code is 4 or 5 digits long and assigned by the FDA. If the name of the labeler is indeed requested for this element, then the title needs to be changed. Should it be the code of the labeler listed in the NDC code?	There appears to be an error in the document and needs correction. Section 4.2.6 and 4.2.7 both indicate entry of the name of the labeler listed in the NDC Code

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	Not applicable to API manufacturers	
4.2.8 Application Type		
4.2.9 Application Number		
4.2.10 NDC Product Code	The NDC Product Code identifies the labeler, the product, the commercial package size, product code for the specific strength, dosage form, formulation of the drug, and the package code for the package size and type. Therefore, by asking for NDC Product Code for every product, FDA is implying that metrics are being segmented not only by product, but by strength and package size/type. Not applicable to API manufacturers	This implication of requesting data at the NDC level is a major divergence from our understanding of what FDA proposed in its draft guidance. If data are required at this level, it will significantly increase the data collection, compilation and submission burden. If FDA is requesting this information for some other purpose, it needs to be clarified. A clarification is needed as to how FDA proposes to handle product codes, and also whether establishments are to report data by product, strength and package size/type. If FDA requires packaged NDC code, this has the resultant potential to increase complexity and consequently burden. It is important to have clarity of identification, structure, and format for reporting of data points. For OTC store brand products, NDC numbers are not assigned until the final stage of packaging. Upstream manufacturing is not assigned a single NDC number; therefore, data points from bulk manufacturing have the potential to be allocated to multiple NDC numbers. For example, if the OOS occurs at the bulk tablet stage, we may not know what the final bottle count will be for that batch. In this case how is the OOS data point assigned? In summary, since NDC assignment may occur late in the process perhaps even in different quarters, it may be very difficult to assign metrics at the NDC level. A potential solution may be to use Internal formula codes as being consistent and are normally directly correlated to an APR.
4.2.11	Clarification is requested on the format of	Uniformity between the different regions that will provide data (e.g., US, EU.)

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Time Period Start	the date to be reported (DD/MM/YYYY?)	
4.2.12 Time Period End	Clarification is requested on the format of the date to be reported (DD/MM/YYYY?)	Uniformity between the different regions that will provide data (e.g., US, EU.)
4.2.13 Lots Attempted	ISPE's Wave 2[1] showed Lots Attempted was not correlated to any quality outcomes and was highly burdensome to collect. If this is for each establishment, section 4.3 needs to allow for multiple entries. Alternatively, it should be clear that data points should be provided at the sponsor/applicant level. Add "during time period" A definition is required that "drug" means FDF or API. Alternatively needs be always referenced "drug/API"	Lots Attempted is a very challenging metric to collect as it is currently defined in the draft guidance. ISPE's Wave 2[1] recommendation is to use Lots Dispositioned (or released/rejected) instead. Clarification to avoid misunderstandings
4.2.14 Lots Rejected	Add "during time period". If this is for each establishment, section 4.3 needs to allow for multiple entries. Alternatively, it needs be clearly stated that data points should be provided at the sponsor/applicant level. A definition is needed that "drug" means FDF or API. Alternatively needs be always referenced "drug/API"	Clarification to avoid misunderstandings

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4.2.15 Attempted Lots Pending Disposition	FDA has clarified its definition for this to be only those lots still pending disposition past 30 days as of the last time point of the time period, e.g. 11:59pm on the last day of the quarter. Our understanding from FDA is that this metric is intended to monitor if companies are holding on release decisions in order to make their Lot Acceptance Rates appear better. Although, FDA's definition seems simple in concept, it is complicated in execution in that the query would have to reference a specific time period, which would make this a manual data manipulation as defined here, instead of a simply querying on the cycle time for disposition. Also, this metric is not possible to report until FDA clarifies when the clock starts on disposition. Is it when manufacturing/packaging is completed? Is it when release testing is completed? Is it when all data to disposition the products are in the hands of the release group? Or is it some other start point?	This is an important point to make for three reasons. First, because as described in ISPE Pilot Wave 2 Report[1], counting disposition lots may not always be easy. The ease of generating this data point can vary in terms of challenge and complexity depending on the design of the site data systems such as SAP, LIMS, etc. Second, with some data systems, it is much easier to simply query on the cycle time of batches dispositioned over the time period, than it is to run a query at a specific time point that takes a snapshot of the age of open batches. Third, the burden associated with this metric will be determined by what FDA specifies as a starting point and whether or not the timestamp for such transactions is captured in a current electronic system. A simple solution is to defer this data point in the initial phase as requested in ISPE's response to the draft Guidance[2]
4.2.16 Out of Specification (OOS) Results – Finished Drug Product or API	It is important to clarify for the user that where the guide states "for each establishment" it really means for each product for each establishment for each quarter.	Wherever the guide states "for each establishment" it needs to define the full breakdown of the data point in order to make it clear and make the effort required for said segmentation apparent.

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	Would this include stability tests based on 4.2.17? It will be beneficial to define somewhere that "drug" means FDF or API. Alternatively, should, be always referenced "drug/API"	Clarification / specificity recommended Clarification to avoid misunderstandings
4.2.17 Number of Lot Release and Stability Tests – Commercial Use	Suggest changing to: '…number…. of tests conducted…' as in draft Guidance. It will be beneficial to define somewhere that "drug" means FDF or API. Alternatively, should be always referenced "drug/API"	Revise description to the number of tests (release and stability) conducted for drug referenced in 4.2.1 for each establishment. Clarification and to avoid misunderstandings
4.2.18 Out of Specification (OOS) Results Invalidated	The FDA's definition in the draft guidance specifies that "Invalidation of a discrete test result may only be done upon the observation and documentation of a test event that can reasonably be determined to have caused the OOS result." The requirement for "observation' is in our experience impractical, as most laboratory errors are never "witnessed" as they occur. Would this include release tests?	NOTE: ISPE recommends that FDA maintains the details on definitions and examples in the overall Guidance and have the Guide focus on submission of same, as opposed to repeating definitions and having potential inconsistency between the two documents. Alternatively, the possibility exists that FDA may combine the two documents thereby precluding redundancy and potential inconsistency. The requirement for witnessing an error as a criterion for invalidating a test needs to be reconsidered and we recommend removed from the definition. Clarification is requested regarding reporting data if the establishment does not

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		perform all testing, as for example in a Contract Test Laboratory case.
	More clarity is required regarding the definition of the cause of the Invalidated OOS result and about how the metric is calculated	A number of causes (e.g. method error, analyst error, not following procedure, etc.) could be being tracked and there is a need to agree on which causes would fall into the FDA laboratory error category,
	A definition is needed that “drug” means FDF or API. Alternatively, should be always referenced “drug/API”	Clarification to avoid misunderstandings
4.2.19 Product Quality Complaints	The definition needs to be not by product, but by product family. This is because very often the complaint submitter does not know the exact product code, lot or still possess the package information. Usually they know the general product family.	If FDA defines this metric as by product, for example at the labeler level, then many complaints will not be able to be reported or it will be inaccurately reported by forcing companies to assign a general complaint about a product to a specific product code as a guess. The solution is for FDA to allow complaints to report complaints by product family.
	What does "all establishments" mean in 4.2.19 – all covered establishments? It is not clear what is meant "across all establishments." in this section.	Clarification needed about ‘across all establishments’.
	This field is marked as required, however it is not clear how to populate it while being compliant with line 824 from “Request for Quality Metrics Guidance for Industry” which states “*This element should not be segmented by establishment and only one value should be reported per quarter. This value should*	Clarification requested

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	represent all product quality complaints received for the drug referenced in (1), above. It can be attributed to the Reporting Establishment or one of the other establishments listed in the table. If attributed to one of the establishments listed in the table, the Reporting Establishment does not need separate rows" Is it 'Number of product quality complaints received in the United States' pertaining to the lots of a product distributed in the United States or 'Number of product quality complaints received in any market that relate to a product distributed in the United States'? For APIs, the sum of product quality complaints needs not be restricted to the batches distributed to US, but be world-wide.	Clarification requested US may not be the biggest market and API manufacturers do not always know the final shipment place of the Finished product.
4.2.20 Lots Attempted and Released	Change to "Lots Released"	Lots attempted is already identified in 4.2.13. The calculation proposed in the draft Guidance for Product Quality Complaints Rate includes 'lots released' in the denominator. The definition should be clear.
4.2.21 Annual Product Review (APR)/ Product Quality Review (PQR) Completed		
4.2.22	Clarification is required for "number of	We request clarity and recommend flexibility on what this statement intends. An

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Annual Product Review (APR)/Product Quality Review (PQR) Required	APRs for the product". Should each product have one single APR from a site and what is the definition of a product – one formula, one strength, one strength in each pack type or pack size? Clarification is required whether or not this metric is per covered establishment	APR/PQR could be per establishment per product dosage form (e.g. vial, tablet, capsule, suspension, etc.). For many companies' multiple strengths for a product dosage form may be combined into one APR. In some cases, companies do have one APR per strength.
4.2.23 DUNS Number	Do all establishments have a DUN and Bradstreet DUNS? Some non-U.S. establishments listed as in-scope for this guide in the draft guidance, may not have a DUNS number? Are both DUNS and FEI numbers required?	Clarification is requested as how to handle this entry in cases where a site does not possess a DUNS number. Clarification is desired as to why both numbers are required.
4.2.24 Dosage Form	A single product can be manufactured in different dosage forms. Therefore, this implies the FDA wants establishments to segregate data by product and by dosage form.	Clarification is requested as to the intent of reporting Dosage Form and how data should be segregated – please also see comments under section 4.2.1
4.2.25 Facility Establishment Inventory Number (FEI)	See comment in 4.2.23	
4.2.26 Establishment Activity Classification	The usefulness of this data element as free-text is limited without a standard naming list of options (e.g. Manufacturer, Repackager, Relabeler). As a free-text field, establishments can report varying classifications for the same type of	Without a standard list of options, FDA will be challenged to compile and search the data. The solution is for FDA to supply a standard list of options to enter for the classification.

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	activity and FDA will not be able to reconcile the establishment classification.	
4.3 Mandatory Data Elements - Formats	1. MONOGRAPH – It is recommended that this is not be left as a free text field. FDA could provide standard lists for establishment to choose from, otherwise, FDA will receive data it cannot import without manual manipulation.	FDA needs to provide a standard list of options for MONOGRAPH
	2. LABELER and NDCCODE – Is this always Numeric or is it Alphanumeric?	If these are alphanumeric then they need to be designated as such
	3. TIMEPRD – is listed as the code for both Time Period Start and Time Period End. It cannot be both. This is a typo.	TIMEPRD is a typo – correction is needed
	4. APRWIDD – is listed as the code for both Attempted Lots and APR/PQR Completed. It cannot be both. This is a typo.	APRWIDD for Attempted Lots is a typo and it needs be corrected
	5. APRWIDD – recommend FDA spell out the entire word “Yes” or “No” instead of using “Y” and “N”.	In some languages, “Yes” is abbreviated “N” and vice-versa. If the guide is to be used by companies outside of the U.S., then it should not follow American naming conventions.
	6. DOSAGEFORMS – we recommend that this is not be a free text field. FDA needs to supply a list of entry options for this. The data element name “DOSAGEFORMS” has more than 8 letters.	FDA needs to provide a standard list of options with 8 or less characters.
	7. ACTIVITY – this would be easier to deal with if it is not a free text field.	It is suggested that FDA provides a standard list of options

GUIDE SECTION	COMMENT(S) AND ANY RECOMMENDED ALTERNATIVE TEXT	RATIONALE Where appropriate
	FDA could consider supplying a list of entry options for this 8. Time period start and time period end have the same Data Element Name. Is this correct? 9. FDA is asking for data by "QUARTER", but it was understood that data would be submitted annually and report the quarterly increments. In addition, the definition of Quarter is not clear. Is it calendar quarter, an FDA generated quarter or related to the APR cycle? 10. Some elements that are identified as numbers, are not numbers used for calculations, but numbers used as identifiers. This needs to be clearly noted. This applies to: LABELER, DUNSNUM, FEINUM.	There could be confusion between the APR and quality metrics cycle, which could lead to much redundancy.
4.4 Optional Data Elements - Descriptions	In its response to the draft Guidance ISPE[2] recommended that Optional Data Elements are deferred. Some further comments are given below.	Detailed rationale is given in ISPE's response to the draft Guidance[2]
4.4.1 APR Approval	The user will benefit from clarification that this section is related to all batches manufactured independent from the final shipping destination (US and ROW), at least for API manufacturers	For API manufacture, it is difficult to know where each batch was commercialized/shipped to after it is transformed in FDF. FDF Pharmaceutical companies may not provide that data to the API supplier.
4.4.2 APR Approval by Quality Unit	Clarification is requested on what FDA means by "head of Quality unit", and "head of operations unit".	For some organizations, this language could cause confusion, and/or could be reported in a manner that could not show the intended level of quality performance. There is a wide range of titles across industry at both site and corporate levels.

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and/or Operations Unit		
4.4.3 Percentage of Corrective Actions and Preventive Actions (CAPA) Involving Re-training	There could be unintended consequences of this as a metric e.g.: Drive companies to simply mandate that the term “re-training” may not be used in any CAPA. Drive companies to not re-train people when they really do need to be re-trained Drive companies to simply game the metric by designating all re-training as new training, by issuing a new training ID for the module. Penalize companies who list re-training as one of many measures being taken on a CAPA. For example, if I redesign the process to make it impossible for a mistake to be made and then re-train the people on the process then it counts as re-training, which FDA could consider ‘bad’, even though I did the right thing. To consider the “estimated percentage” since this leaves a lot of "personal" interpretation.	This metric is very problematic as it is easily gamed, it appears to suggest that all re-training is inappropriate and will not drive better CAPA performance as intended by the FDA. ISPE recommended that FDA defer this as a metric. For example, there can be situations where retraining is a part of the CAPA, but not the root cause? This is still "involving". Further clarification is recommended.

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4.4.4 Process Capability (PC) or Process Performance (PP) Index Calculation		
4.4.5 CAPA Trigger Policy		
4.4.6 Triggers for CAPA	The value of this metric is difficult to interpret without the unit of measurement i.e. the context of what process capability or performance index is being used?	For example, if the trigger is 0.99 and this refers to Cpk then that is not very good, and If refers to Ppk, then it is marginal. If it is a percent acceptance (which could be considered a process performance index) then it is good and if it is defects per million units (DPMU) then it is world class. It is not valuable to try to compare trigger values related to difference types of process measurement. This metric is considered of limited value unless the intended definition was different. ISPE recommended deferring this as a metric in its current definition.
4.5 Optional Data Elements – Formats	CAIRTP – It is not clear how this field should be populated. For example, if the answer is 5.7%, then is the number submitted 5.7 or 0.057? PCPPCAPA – This field needs be reconsidered if it should be a numeric field (see comments on 4.4.3 above) “APRAPPVDY” has 9 letters, when it should have 8, per Table 1, section 3.1	CAIRTP – clarification is requested as to how data should be entered in this field. PCPPCAPA – the numeric value is insufficient to put the number in the proper context (see comments on 4.4.6, above)
5 DATA	Further clarity and definition is required and needs to be circulated for public	It is important in our view that the validation rules should be commented on by industry before they are made final. Allowing industry to review the validation rules in advance

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VALIDATION RULES	comment before the Guide is finalized	and provide feedback based on its understanding of the nuances of its unit operations and processes aligns with FDA's stated objectives for the guide.
6 GLOSSARY		

References

1. ISPE Quality Metrics Initiative Quality Metrics Pilot Program, Wave 2 Report, http://www.ispe.org/quality-metrics-initiative

2. International Society for Pharmaceutical Engineering. "ISPE Response to FDA Federal Register Notice on Quality Metrics [Docket No. FDA-2014-D-2537] and Draft Guidance, Request for Quality Metrics, 27 July 2015." 24 November 2015. http://www.ispe.org/global-regulators/ispe-comments-regulations

3. ISPE Quality Metrics Initiative Quality Metrics Pilot Program, Wave 1 Report, http://www.ispe.org/quality-metrics-initiative