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Connecting People, Science and Regulation®

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March 27, 2017

Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Reference: FDA Guidance for Industry Request for Quality Metrics
Docket: [FDA-2015-D-2537-0097]

Dear Sir/Madam:

PDA is providing comments on the latest revision to the FDA Quality Metric Guidance document.

PDA is concerned that there remain questions on metric definitions/data points and logistics that need to be resolved before companies can prepare data for submission during the voluntary phase. PDA believes an additional Question and Answer document addressing the comments received to the revised draft will further help to clarify the request and encourage firms to participate in the voluntary phase of submitting data. To that end PDA has enclosed a listing of all the questions collected from participants at the 2017 PDA Metrics and Culture Conference held on February 21 and 22. PDA further encourages FDA to hold another public meeting on the topic of Metrics.

PDA would like to emphasize that the FDA consider the importance of the trends of each of the calculated metrics rather than compare individual results from one plant site or one company to another. As noted in previous PDA comments to the original draft guidance, because of the great diversity across manufacturing operations and product types, a straight comparison of data points may not provide valuable or operational information for the risk based model of inspections. PDA's detailed comments on the draft guidance are enclosed.

If there are any questions, please do not hesitate to contact me.

Sincerely,

Richard M. Johnson

Richard Johnson
President & CEO, PDA

CC: Richard Levy, PDA; Denyse Baker, PDA

Food and Drug Administration Draft Guidance
Request for Quality Metrics Revised Draft
March 27, 2017

General Comments	Rationale	Critical Comment?
1. As noted in previous PDA comments on the Metrics Draft Guidance; PDA suggests that FDA define the success criteria for the voluntary phase of the quality metrics program. This could entail a number of assessments against expected outcomes with results reported back to industry, and could include: a. Applicability: Metric and definitions are applicable across the industry – During the assessment period, allow firms to submit comments on why the current metric assessment and / or metric definition are not applicable for their product. Assessments should include a reporting percentage of missing metric data due to nonalignment of product type with metric definition. Is there a need to modify or clarify metrics or definitions to encompass entire industry product populations based on submitted comments during the assessment period? b. Differentiation: Ability of the data to differentiate sites / products–Does the metric data allow the sites to be categorized as quality higher risk sites or lower risk sites?	This proposal will establish common understanding between FDA and industry on the goals of the voluntary phase as well as help assure the success by assessing five areas and making the appropriate modifications to evolve the program, or determine the value is not worth the extra burden to industry and FDA.	

General Comments	Rationale	Critical Comment?
Assessment: Use statistical tests to show relevance of data by generating a population curve from high quality to lower quality sites. FDA to identify the number of sites that would have seen a reduced inspection burden if the data had been used in the inspection risk-based model. c. Reporting assessment: Is the reporting optimized to minimize industry's ongoing burden (man-hours) for submission and FDA's use of the data? Allow firms to submit suggestions on optimizing collection of data. Assessment: Assess optimization suggestions and rerun the burden assessment with an independent firm to provide an updated value and more realistic value. FDA to outline the working assumptions on additional burden activity beyond existing GMP data collection. What would be the proposed benefit for FDA, patients, and Industry to offset this increase resource burden? This might include estimated resource saving from fewer inspections, faster post-approval changes, identification of potential drug shortages, and a possible shift in the two-year assessment period on improved metrics of higher risk sites / products. d. Assessment of Unintended Consequences: gather evidence (i.e., 483 observations, specific		

General Comments	Rationale	Critical Comment?
information and data from a site, etc.) from inspectors and industry about observed unintended consequences and whether these can be mitigated. Assessment: Examples of unintended consequences shared from FDA and Industry to determine if mitigation is needed. Harmonization Assessment: Are other regions requiring the submission or developing the submission of metric data. What efforts need to be addressed to harmonize metric reporting globally before FDA's program is used officially? It is suggested that this milestone evaluation be in the form of a public meeting to share FDA's assessment and industry's experience during this initial "assessment period", and determine whether any adjustments to theprogram are appropriate prior to full implementation into FDA's inspection risk-based model.		
2. Metric definitions appear in Section B as: LAR, PQCR, IOOSR. The data that may be reported appear in Section C as LAR, IOOSR, PQCR. PDA recommends putting both sections in the same order for clarity.	Will improve readability of the guidance document.	
3. PDA recommends FDA clarify that the current definitions from the revised draft guidance will be used for the voluntary data collection phase and what content from the initial Technical Conformance Guide will apply.	This will enable sites / firms begin to align and plan their participation based on the current revised draft and be better prepared to submit data once the collection period begins in January 2018. Firms are already collecting 2017 data based on current definitions and changing late in the year will be difficult to accommodate.	Yes
4. PDA recommends FDA specify what benefits related to inspectional risk model or for post approval change reviews will be available to the participants in the voluntary phase.	It is not clear what the benefits might be for sites participating in the voluntary program. FDA implies that it depends on the number of participants and the analysis of the data. PDA	

General Comments	Rationale	Critical Comment?
	recommends the FDA provide reduced inspection frequency and/or reduced PAC reporting categories for those participants who willingly participated in the metrics program. In PDA's opinion by clarifying any benefits, FDA will encourage more companies to participate. Maximizing the number of participants should strengthen the potential learning during this voluntary phase.	
5. With respect to the proposed reporting Tier proposal, PDA agrees that there should be some external recognition for participants in the program to acknowledge the fact that they have invested significant time and resources to assist FDA in evaluating the benefits and cost of requesting metrics. However, FDA's "reporters list" model is somewhat complex and could disadvantage larger firms with more complex supply chains and larger product portfolios or reliance on CMOs where existing quality and business agreements do not cover the exchange of metrics data. The Tier reporting approach should not be enacted before the guidance is finalized.	PDA is concerned that setting this tiered-approach may in fact, discourage companies from reporting at all during the voluntary phase because of a concern they would not end up in the top tier. PDA recommends as an alternative that FDA recognize each firm who has submitted either a product report or site report by publishing a list of these firms or sites. PDA believes this approach will encourage more firms to participate by alleviating their concerns about not being able to achieve the currently defined "top tier." PDA also believes it is important to provide some recognition for those firms/sites that are making the effort to assist FDA in learning how best to implement the metrics effort.	
6. It is not clear how long the portal will remain open for submission of metric data.	To facilitate metric reporting, PDA recommends the portal remain open for all of 2018 to facilitate alignment of metric submission with an internal site's Annual Product Reports. In order to avoid delay in learning from the metrics data, PDA suggests FDA could consider an interim analysis of received data after one quarter or at mid-year rather than waiting for end of submission window.	Yes
7. PDA appreciates that FDA has heard the earlier concerns and created an opportunity for firms/sites to correct errors discovered after the metrics data submissions. However, the use of an email address as listed in the FR notice is neither controlled nor specific enough. A more formal system should be developed and integrated into the final guidance.	To ensure data integrity, the error correction process should be more controlled and there should be a positive feedback that FDA has received the correction and implemented it. Email is not controlled and specific enough. The submission of a correction should be controlled and not just available to anyone who can send or receive email.	

General Comments	Rationale	Critical Comment?
8. PDA asks FDA to be an advocate for global harmonization on the topic of metric data collection and encourages FDA to continue to reach out to other global health authorities as the program is being developed.	Because of the global nature of pharmaceutical manufacturing and supply chains, having a harmonized set of metrics to report to avoid proliferation of similar initiatives from other agencies.	
9. PDA recommends that FDA establish a Q&A Document to clarify ongoing issues prior and/or during the pilot phase of the metrics program and has provided a list of suggestions questions at the end of this comment document.	Use of the Q&A vehicle	
10. As written the document implies that contract labs and CMOs would have to provide data reports by product to their clients and separate data reports by site to FDA. PDA recommends that whoever holds the license be responsible to supply the data. CMOs would provide data to their clients(contract givers) and these clients would submit.	CMO data could likely be incomplete because they don't have visibility to a complete data set.--such as complaints--or may not be performing all of the analytical tests so won't have all the OOS data. Another concern is that a CMO may be listed in a license or marketing authorization without their knowledge creating reporting requirement of which they have no awareness. PDA recommends the reporting responsibilities are better defined in quality agreements.	
PDA recommends that a comment field be available for each data element rather than just one comment field for the entire submission.	Three hundred words is not sufficient enough to provide context for 11 data elements with all the rows. One comment per row would allow a submitter to be more specific with an explanation.	

Specific Comments to the Text

Line No.	Current Text	Proposed Change	Rationale	Critical Comment?
41	The voluntary reporting phase of the program described in this guidance is not focused on reporting from certain CDER regulated manufacturers (i.e., compounders operating	The voluntary reporting phase of the program described in this guidance ~~is not focused on reporting from~~ **does not apply to** certain CDER regulated manufacturers (i.e., compounders operating under section 503A or registered as	To clarify what type of manufacturing sites and products should be part of the voluntary program. It would be helpful for FDA to indicate whether these types of sites will be included at a later point.	

Line No.	Current Text	Proposed Change	Rationale	Critical Comment?
	under section 503A or registered as outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) or CBER regulated ….	outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) or CBER regulated ….		
115	FDA does not intend to take enforcement action based on errors in metric data submission "provided the submission is made in good faith".	PDA recommends the following language: "…provided the submission is made ~~in good faith~~ with appropriate checks and balances such as a functioning Quality System in place."	The statement "in good faith" needs clarification. In this way errors could be differentiated from intentional falsification.	
122 and 118	FDA intends to analyze the calculated quality metrics to support its understanding of the safety risks of manufacturing establishments and products.	PDA recommends adding a foot note to clarify the meaning of safety in this context.	PDA understands that this language is taken from the recent legislation modifying language in FDA Act 21 US Code 360 (h) (3). However "safety" could be misinterpreted to refer to clinical or pharmacovigilance considerations which are not in the scope of this guidance document.	
218	LAR = the number of accepted lots in a timeframe divided by the number of lots started….in the current reporting timeframe.	LAR = the number of released lots ~~in a timeframe~~ divided by the number of lots started…in the current reporting timeframe.	Changed "accepted" to "released" for consistency within the document as "accepted" was only used in line 218 and in the definition (lines 592-603). All other references to acceptable lots refer to them as "released" lots. Inclusion of "in a timeframe" within the definition is confusing as the definition also ends with "in the current reporting timeframe".	Yes

Line No.	Current Text	Proposed Change	Rationale	Critical Comment?
225	Invalid OOS Rate	PDA recommends that sampling error be included in the count of OOS even if samples were pulled by non-lab personnel.	PDA observes that "sampling error" is somewhat in-between manufacturing and measurement processes. So we would suggest improving the clarity here by appointing sampling error to either one or the other.	
221	Product Quality Complaint Rate 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.	**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~~ **packs for commercial distribution** ~~distributed~~ in the current reporting timeframe.	PDA recommends calculating complaint rate using number of packs for commercial distribution rather than individual dosage unit. Because of the variability in some presentations PDA is concerned that dosage unit is not the correct reference for reporting complaints. (e.g. inhaler product with multiple doses in a single unit; variable number doses consumed from a bottle of oral liquid; or multi-dose syringes given based on patient weight). Calculating rate based on saleable unit is more manageable and quantitative.	Yes
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).	Reporting of data should include all manufacturing operations, including testing, which would be included in a PPR as saleable lots. For purposes of this guidance "Saleable lots" **are** defined as "lots intended for commercial distribution, post-**approval clinical trial lots** when the same manufacturing process and controls are used as for commercial lots." This does not	Using this paragraph to clearly define "saleable lot" serves to clarify much of the remaining section.	

Line No.	Current Text	Proposed Change	Rationale	Critical Comment?
		include lots **for other purposes** such as **qualification or engineering runs.**		
302	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…	We recognize that there are rare instances when this construct will not be valid (e.g., lots pending disposition for an extended period, **or lots aborted during manufacturing**) and we…	PDA recommends adding an additional example of events that could affect the general assumptions described in this bullet and adjusting the definition of "rejected lots" to include aborted lots for consistency.	
324	For the purpose of the quality metrics program, the following OOS results should be counted: (1) finished drug product and API and long-term stability test results only…	For the purpose of the quality metrics program, the following OOS results should be counted: (1) finished drug product and API **lot release, including in-process tests that act as a surrogate for a lot release test[52],** and long-term stability test results only…	For clarification PDA recommends added text from definition that further defines the criteria for data to be counted so that all criteria are located together instead of in several places in the document. Relocation should also include relocation of footnote 52.	
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.	For the purpose of this program, an OOS result should be counted on the day that an **OOS investigation is completed** and the test result is **invalidated by the Quality Unit.**	It is not reasonable to count an OOS result on the day that the test result is completed or the day that an OOS investigation is initiated, since, in both cases, a decision may not have been made by the Quality Unit to invalidate the test result due to an aberration of either the measurement process or manufacturing process. Any Result not invalidated (i.e. a confirmed OOS) would not be reported in this metric.	Yes
361	Product Quality Complaint Rate (PQCR)	PDA recommends that the guidance be clarified that **complaints**	Complaint rates between products and companies will be very hard to compare	Yes for combo product

Line No.	Current Text	Proposed Change	Rationale	Critical Comment?
		against any kit components be counted in the total rate. Alternatively this example could be included in a future Q&A document.	because of the great variability in product types, seasonal variation, etc. In PDA's opinion it is simpler to count all complaints than try to split out product specific complaints from component complaints. PDA also recommends that for a drug/biologic device combination product that complaints that are within the scope of the guidance only be counted and reported. i.e. complaints against the drug/biologic portion of the combination.	complaints
592	Accepted Lot	~~Accepted~~ Released Lot	PDA recommends changing "accepted" to "released" for consistency within the document as "accepted" was only used in line 218 and in the definition (lines 592-603). All other references to acceptable lots refers to them as "released" lots.	
593-596 (also 284-303)	If the lot is released with an unexpectedly low yield due to an assignable root cause and the associated investigation supports the release of the lot, it should be counted as a released lot.[46] Investigations into low yield results should be thorough and managed by the quality unit.	~~If the lot is released with an unexpectedly low yield due to an assignable root cause and the associated investigation supports the release of the lot, it should be counted as a released lot.[46] Investigations into low yield results should be thorough and managed by the quality unit.~~	PDA recommends moving this text from definition to section on specific criteria for the LAR data (lines 284-303) as a new bullet point as this text described criteria for counting lots that is not already in the list of criteria. Relocation should also include relocation of footnote 46.	
596-597	If a lot number is closed,	~~If a lot number is closed, the lot is~~	Similarly, PDA recommends moving this from	

Line No.	Current Text	Proposed Change	Rationale	Critical Comment?
(also 284-303)	the lot is transferred to a new lot number, and subsequently released, only the original lot should be counted.	~~transferred to a new lot number, and subsequently released, only the original lot should be counted.~~	the definition to the section on specific criteria for the LAR data (lines 284-303) as a new bullet point because this text described criteria for counting lots.	
597-603 (also 284-303)	An accepted lot should be counted on the day of the final disposition decision. 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.	~~An accepted~~ **A released** ~~lot should be counted on the day of the final disposition decision. It may be possible that an accepted~~ **a released** ~~lot is no longer considered accepted~~ **released** ~~(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~~ **a released** ~~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.~~	As noted above PDA recommends moving this text from the definition to section on Specific criteria for the LAR data (lines 284-303) as a new bullet point as this text described criteria for counting lots. In addition, for consistency, PDA recommends changing "accepted" to "released" for consistency within the document as "accepted" was only used in line 218 and in the definition (lines 592-603). All other references to acceptable lots refer to them as "released" lots.	
607-610 (also 284-303)	If the manufacturing spans multiple time segments (quarters), the started lot should be counted when	~~If the manufacturing spans multiple time segments (quarters), the started lot should be counted when the lot number is issued or~~	As noted above PDA recommends moving this text from definition to section on Specific criteria for the LAR data (lines 284-303) as a new bullet point as this text described criteria	

Line No.	Current Text	Proposed Change	Rationale	Critical Comment?
	the lot number is issued or the API or primary starting material is physically charged.	~~the API or primary starting material is physically charged.~~	for counting lots.	
610-611 (also 284-303)	If unique lot numbers are issued for different packaging configurations, each lot number should be counted.	~~If unique lot numbers are issued for different packaging configurations, each lot number should be counted.~~	As noted above PDA recommends moving this text from definition to section on Specific criteria for the LAR data (lines 284-303) as a new bullet point as this text described criteria for counting lots.	
620-623	For the purpose of the quality metrics program, the following test events should be counted: (1) lot release, including in-process tests that act as a surrogate for a lot release test,[52] and long-term stability test results *only* and, (2) all lot release and long-term stability test results, even if the source of the OOS is later determined to be due to a measurement aberration.[53]	PDA recommends deleting this text.	The criteria described in this text are already included in section on Specific criteria for the IOOSR data (lines 320-359). Removing the duplicate text improves the clarity of the document.	
628-631	For the purpose of the quality metrics program, the following test events should be included: (1) lot release[55] and stability test	PDA recommends deleting this text.	The criteria described in this text are already included in section on Specific criteria for the IOOSR data (lines 320-359). Removing the duplicate text improves the clarity of the	

Line No.	Current Text	Proposed Change	Rationale	Critical Comment?
	results *only* and, (2) all lot release and stability test results that initially appear as OOS, even if invalidated by a subsequent laboratory investigation.		document.	

Please see the additional attachment for a listing of questions collecting during the 2017 PDA Metrics and Culture Conference. PDA is providing these as a convenience for FDA and encourages FDA to respond publically in advance of the voluntary phase so as to assist industry in preparing as fully as possible and to maximize participation.

Food and Drug Administration Draft Guidance
Request for Quality Metrics Revised Draft
March 27, 2017

The following questions were collected from participants in the 2017 PDA Quality Metric Conference and are offered here for the consideration FDA in developing a Q&A document for Quality Metrics and/or the final guidance document. PDA will also submit these questions directly to the CDER-OPQ-Inquiries email box. Although some of these questions were addressed during discussions at the conference, PDA has included all of them here for convenience of FDA.

TIMING

1. Does FDA plan on conducting the voluntary phase with the revised draft guidance (from Nov 2016) or a new revision?
2. What is the projected time the portal window will be open for data submission of 2017 metric data?
3. Please clarify what FDA intends to publish on their website with regards to Metrics participation or results?
4. Clarify the timing for testing phase of the FDA Data Portal prior to launching the voluntary phase.
5. Clarify the timing for issuance of the revised Technical Conformance Guide. Will we have the revised Technical Conformance Guidance before the January submission?
6. Do we have a target time range that we expect the portal to be open for submission of data in 2018 voluntary phase (ie: 1 month, 1 quarter, etc.)?
7. Does FDA plan on conducting the voluntary phase with the current definitions?
8. With respect to the reporting period once the portal is open: If it opens in January 2018, how long will it remain open to collect industry data? Will it accommodate the different data collection time frames used throughout industry?
9. The guidance does not clearly explain how reporting in should be done in terms of reporting data in quarters. The status of batches can change through the manufacturing process which means that the data points reported for a first quarter will change when reporting for the second quarter. E.g. A batch released in the first quarter is changed to reject in the second quarter due to an incident. Reporting for this data can be done in two ways: 1). The first quarter is fixed and the batch will remain with a released status showing the performance of this quarter as a snapshot in time. The same batch is also reported in the second quarter as rejected. 2) The information on the released batch will not be reported as part of the first quarter as the batch information has changed to rejected but in recorded only in the second quarter. The last reporting will therefore show how all batches ended up whereas the first will give a picture of how a quarter look like.
10. What is the expected timeframe for mandatory participation?

BENEFITS AND INCENTIVES

11. What are the benefits for sites / firms participating in the voluntary phase?

12. Will data during voluntary phase be incorporated as a factor in surveillance inspection model or adjustment to post approval changes?
13. Is publication of the tiers just for voluntary phase or mandatory as well?
14. Can the FDA please provide more detail or a specific scenario example for how the reduced post-approval change management program will operate for those sites seen to be "lower risk"?
15. How would CMO sites submitting reports expect to see any post-approval change relief related to the metric reporting, especially when they are performing contract work for the product license holder? Does the PAC relief relate to the site or license holder?
16. What should sites, participating in the voluntary phase, anticipate regarding less frequent inspections?
17. How does FDA intend to capture the benefit-burden of the program as part of the evaluation and in advance of rule-making?
18. What is FDA trying to accomplish with implementing the metrics - for the agency AND for the industry? What sort of behavior within the industry are they hoping to see? And how will we know if/when we have succeeded?
19. Could you elaborate on how the reduced inspection frequency will work? Will this also be applicable for foreign companies and CBER products?

SCOPE AND PARTICIPANTS

20. Please clarify whether company specific metrics data would be subject to FOI request or if it would be considered proprietary information?
21. How will combination products be addressed?
22. Does the FDA expect data to be reported for the following product types?
    a. Re-usable Devices
    b. Assembled combination products
    c. Intermediates of APIs
23. There have been rumblings of use of metrics for medical device - how will that fit in or be implemented?
24. Are there plans to add additional metrics after the mandatory phase is initiated and would this include some type of Process Capability questions as proposed in the 2015 draft?
25. Would FDA consider excluding non-dose limiting OTC products from the metrics program based on the very low risk to public health and the high number of different products and frequent new launches leading to high complexity for reporters?
26. Could FDA apply role based categories similar to those negotiated in GDUFA II for the metrics program; Such as exempting non-product license holders from site reporting?
27. Referring to Line 41 of the revised draft guidance which says the document "is not focused on" certain CDER regulated manufacturers; Should these "certain regulated manufacturers" begin to establish metric reporting programs to align with FDA draft guidance in

anticipation of possible future inclusion or is it the FDA's intention that these entities will remain out of scope?

28. Is the data requested just for drug intended for U.S. use or for all lots manufactured?
29. What is the expectation for addition of a newly approved product, a transfer to another site or CMO divestment of a product to a new owner?
30. Pertaining to biologics:

    a) What is meant by in-process lots? (Unlike the tablet example, quality decisions are made on lots up through Final Drug Product.)

    b) What is meant by "lots intended for primary packaging"? Is this material which when further processed will be filled into primary packaging or is this Drug Product only?

    c) Is Bulk Drug Substance in scope?
31. The guidance seems to indicate that CMOs that provide data to their clients to be included in product reporting must also complete their own site reporting. Doesn't this lead to duplication of data submission to FDA (and increases the burden on the site)?
32. Many products are manufactured in multiple strengths of the same active ingredient and packaged into multiple sizes (i.e., 30 count bottle and a 100 count bottle). Should these data be bundled as one product when reporting by product or broken up by strength and count?
33. Have FDA considered requesting metrics similar to the EU whereby they are collected according to a site's current definitions ahead of an inspection? (Instead of standard metric rates/definitions). Sites already have this data as it is included in current inspections and and PPRs. (Deviations, OOS, complaints, rejections...)
34. Further clarification and examples needed on how to interpret Product Family definition for finished drug products related to reporting on National Drug Code (NDC).
35. Can e.g. a drug product with different strengths or same drug with different device be grouped into a family even if they have different NDC codes for simplicity?
36. How will access to the portal be granted? Will anyone from a company be able to submit or will there be limited access? Will sites have to validate the transfer of data to the FDA?
37. Why the vaccines are out of scope?
38. Would the FDA welcome partial reporting from a company? For example a company might choose to contribute data from one product or site where the reporting structure is in place; however might struggle with CMO's or other sites that have other systems. I think it would be a shame if that company opted out of reporting all together and would think it better to contribute parts of their data. However I would like to hear if the FDA shares that approach?

PRODUCT OR SITE REPORTING

39. If an API and DP is made in the same establishment, is it possible to do one single product submission including the API and the DP or are API and DP submissions by definition 2 separate reports?

40. The FDA guidance discusses reporting by product and by site. Would it be considered acceptable to report some of the measures, such as OOS and Complaint rate, by product but the Lot Acceptance by site? Based on our data systems, some measures will be easier to separate by product than others.
41. The guidance uses both "site" and "establishment" yet only Establishment is defined. Does FDA intend these to be synonymous terms or please explain the difference between site and establishment in the draft guidance?
42. Is the expectation when data is submitted it comes directly from a site within an organization or from a central source representing all the sites within the organization?

DATA VALIDATION AND ANALYSIS

43. What type of validation are you planning on for your data collection? Validated system or more traditional "people" review of the data?
44. What will be FDA's requirements with regard to validation and qualification of platforms used to report metrics and data lakes? Does FDA expect pharma to qualify cloud based infrastructures from Amazon, Google or Microsoft?
45. Alex, great presentation. Would you be sharing the data analysis techniques that will be used to assess data submitted by industry (e.g regression analysis etc)? It would be beneficial if manufacturing sites could benchmark and follow the same approach in parallel.
46. What will FDA do with respect to staffing to analyze the data? Will headcount be increased?

DEFINITIONS - OOS

47. If the root cause of an invalid OOS were determined to be sampling error in the manufacturing operation where samples are not pulled by laboratory personnel, should this be counted against this laboratory metrics? Should the invalid OOS focus on lab errors that lead to the invalid result?
48. Should all stability testing be included or just routine stability testing conducted on the annual batch? For example, an investigation leads to a batch being placed on stability. Would the stability testing of that batch now be included in the reporting?
49. If a test requires replicates, and an OOS result is obtained on one of the replicates, but the overall test result (e.g., average) is not OOS. Does the replicate result need to be tallied into the overall IOOS rate?
50. Does the Invalid OOS metric include any error in testing, sample preparation, calculations, instrument issues, analyst error, and almost any error that may invalidate a result or just analyst errors?

DEFINITIONS - COMPLAINTS

51. Does FDA expect firms to include complaints against kit components, which are not the drug product (dosage cup, alcohol wipe, WFI, empty syringe, etc.) in the reported number of complaints by product?

52. How should one report a complaint rate by dosage unit for an inhaler or liquid product with multiple doses in a single container and with some variability in how many doses a patient actually takes?
53. Can PQCR be reported as the number of complaints per 'unit of use' rather than dosage unit in order to address methods of packaging (e.g., blister pack, or titration pack)?
54. The definition of PQC in the Guidance includes the assessment of identity, strength, quality or purity of the product. When complaints do not concern identity, strength, quality or purity, do they have to be included in the report?
55. The denominator for complaint metrics is the number of dose units. The number of dose units is sometimes difficult to determine (e.g.. Inhalers, creams...) wouldn't it be easier to take the number of units sold as the denominator? This would also be supported by the fact that a lot of complaints are on the packaging defects.
56. How should complaints on combination products be reported? Should we report the product complaints separately from the complaints linked to the devices as the number of device complaints is generally much higher than product related complaints.
57. Can multi dose vials be counted as one individual dosage unit for complaint rate metric?
58. Clarification needed on how to report number of product quality complaints received for the product and total number of dosage units distributed for the product related to either the by site or by product reporting dimension. Example: A customer complaint for a product can be registered in many ways. Question on what site /part of the manufacturing process will be reporting the data. A customer complaint will be registered on a packaging batch. Root cause can be found to be traced back to a batch at a different stage of the manufacturing process and a different site. What site will report the customer complaint data? And correspondingly if a in-process site will report, what dosage unit should then be reported? The dosage units produced particularly for this in-process site even though the product units are not saleable?

DEFINITIONS – REJECTED LOTS

59. Should "aborted lots" not failing any specifications be counted as rejected batches?
60. How should sites report "partial lot rejection" for submitted metric data?
61. If a small portion of a lot which was already approved is rejected, for example when small amounts remain that are close to expiry date, or a damaged container, it is assumed this is not included in the data reported. Is this correct?
62. Regarding LAR: In the draft guidance it is suggested that the number of lots started is usually equal to the sum of accepted and rejected lots. In practice this will not happen as there is a separation in time between starting lots and making the batch disposition. Has FDA thought about this?
63. How to count saleable lots? The practical aspect of marking batches as either saleable or in-process seems burdensome compared to the value added with this reporting. Example of the complexity: a product can be saleable at one stage but the batches produced at this stage

may be split after manufacturing is completed and a portion is intended for sale and another portion is intended for a different type of product version where it continues to next stage of manufacturing (adding e.g. device). In these instances the manufacturing process uses the same process and controls data for lots that are not specifically manufactured for a specific product yet meaning that the report could include both data from lots saleable and lots not saleable.