Submission of Quality Metrics Data

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Tara Gooen Bizjak at 301-796-3257 or (CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2016

Pharmaceutical Quality/CMC
Current Good Manufacturing Practices (CGMPs)

Revision 1

Submission of Quality Metrics Data

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TABLE OF CONTENTS

Submission of Quality Metrics Data Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

Quality metrics are used throughout the drugs and biologics[2] industry to monitor quality control systems and processes and drive continuous improvement efforts in drug manufacturing. These metrics can also be useful to FDA: 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. This revised draft guidance includes an explanation of how the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) intend to utilize submitted data and quality metrics to help ensure that their policies and practices continue to support continuous improvement and innovation in the pharmaceutical manufacturing industry.

In order to achieve these goals, FDA is initiating a quality metrics reporting program.[3] As described in this guidance, FDA is initiating a voluntary reporting phase of the FDA quality metrics reporting program.[4] In the voluntary reporting phase of the program, FDA expects to learn more about a limited set of quality metrics, associated analytics, and improve the FDA quality metrics reporting program.

During the voluntary phase of the reporting program, FDA will accept voluntarily submissions of data from owners and operators of human drug establishments. FDA expects that the large

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.
[2] This guidance uses the terms "drugs" to refer to both drugs and biologics.
[3] FDA issued a draft guidance regarding the collection of quality metrics on July 28, 2015. In response to comments received in the public docket (FDA-2015-D-2537), FDA is replacing the draft guidance published in 2015 with this revised draft.
[4] More details about the timing of the program are in the notice announcing the availability of this draft guidance in the *Federal Register*.

majority of voluntary reports will be submitted by establishments engaged in the manufacture, preparation, propagation, compounding, or processing of finished dosage forms (FDF) of "covered drug products" or active pharmaceutical ingredients (API) used in the manufacture of "covered drug products."[5]

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 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 manufacturers of blood and blood components for transfusion, vaccines, in vitro diagnostics,[6] cell therapy products, gene therapy products, allergenic extracts, human cells, tissues, and cellular and tissue based products).[7]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required. Also, in this guidance, the use of the word *should* is used to indicate an FDA preference to promote consistent reporting and counting of quality metrics data.[8]

II. BACKGROUND

A. Modernization of Regulatory Oversight of Drug Quality and Promotion of Post-Approval Improvements

FDA's approach to quality oversight has evolved in recent years. CDER and CBER are committed to supporting the modernization of pharmaceutical manufacturing as part of the Agency's mission to protect and promote public health. This effort is also part of a long-term strategy to mitigate drug shortages by addressing the underlying causes of shortages, as noted in *FDA's Strategic Plan for Preventing and Mitigating Drug Shortages*.[9] In 2002, FDA launched an initiative entitled "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach," to encourage the implementation of a modern, risk-based pharmaceutical quality assessment

[5] The terms "covered drug product" and "covered establishment" are defined in section III.A.

[6] This guidance is not applicable to biological products that meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

[7] The guidance does apply to licensed biological products that are plasma derived products, including recombinant and transgenic versions of plasma derivatives.

[8] FDA intends to accept voluntary reports with quality metrics data that are inconsistent with the metrics and definitions in this guidance, as well as reports about establishments and products that are not the focus of the voluntary reporting phase of the quality metrics program as described 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. Submissions will be evaluated on a case-by-case basis.

[9] See *FDA's Strategic Plan for Preventing and Mitigating Drug Shortages* at: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf.

system.[10] The initiative was published with several goals, including ensuring that regulatory review, compliance, and inspection policies support continuous improvement and innovation in the pharmaceutical manufacturing industry. Since publication of the Pharmaceutical cGMPs for the 21st Century, CDER has promoted a vision of "a maximally efficient, agile, flexible manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight."[11]

FDA encourages manufacturers to routinely use additional quality metrics beyond the metrics described in this guidance in performing product and establishment specific evaluations.[12] The selected metrics are not intended to be an all-inclusive set of the quality metrics that manufacturers may find useful to assess a product and manufacturer's state of quality.

B. Quality Metrics Data – Regulatory Foundation

FDA understands that establishments involved in the manufacture, preparation, propagation, or processing of human drugs, including oversight to ensure quality,[13] currently use quality metrics as part of the process validation lifecycle and pharmaceutical quality system (PQS) assessment.[14] The metrics described in this guidance could be a part of such oversight.

As described in FDA's process validation guidance, manufacturers depend on information and knowledge from product and process development as the basis for establishing an approach to control of the manufacturing process (i.e., a control strategy) that results in products with the

[10] See *Pharmaceutical cGMP's for the 21st Century: A Risk-Based Approach* at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm137175.htm.

[11] See *FDA Pharmaceutical Quality Oversight: One Quality Voice* at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM442666.pdf.

[12] One type of evaluation is an internal, independent audit and review of processes and procedures to determine whether established protocols and procedures have been followed. FDA's Compliance Policy Guide Sec. 130.300, FDA Access to Results of Quality Assurance Program Audits and Inspections (June 2, 2007) describes our policy that during routine inspections and investigations, FDA will not review or copy these specific reports and records to encourage firms to conduct candid and meaningful audits and inspections. The voluntary submission of quality metrics data described in this guidance will be for specific data that are maintained on-site, routinely reviewed during inspections, and not subject to a request for the results of an internal audit. http://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm073841.htm.

[13] Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) section 711 added text to section 501 of the FD&C Act clarifying that, for the purposes of paragraph 501(a)(2)(B), the term "current good manufacturing practice" includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.

[14] Refer to FDA guidance for industry *Process Validation: General Principles and Practices* (Rev 1). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

desired quality attributes.[15] Once a control strategy has been successfully implemented, manufacturers are expected to maintain the process in a state of control over the life of the process, even as materials, equipment, production environment, personnel, and manufacturing procedures change.[16] Current good manufacturing practice (CGMP) for human drugs require manufacturers to have an ongoing program to maintain and evaluate product and process data that relate to product quality.[17] Best practice for this ongoing assessment is continued process verification,[18] which should include a Periodic Product Review (PPR), conducted at least annually, in which data collected includes relevant process trends and quality of incoming materials or components, in-process materials, and finished products. Some establishments may call this evaluation an Annual Product Review (if conducted annually) or a Product Quality Review,[19] for finished drug products or APIs, respectively. 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.

Under Title VII section 706 of the Food and Drug Administration Safety and Innovation Act (FDASIA) Public Law No. 112-144, FDA may require the submission of any records or other information that FDA may inspect under section 704 of the FD&C Act, in advance or in lieu of an inspection by requesting the records or information from a person that owns or operates an establishment that is engaged in the manufacture, preparation, propagation, compounding, or processing of a drug. The quality metrics data described in this guidance is information of the type that FDA may inspect under section 704 of the FD&C Act. 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. 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.

Section 510(h)(3) of the FD&C Act requires a risk-based inspection schedule for drug establishments according to the known safety risks posed by establishments that are required to register. These risks are based on certain factors described in section 510(h)(4)(A-F), including the inherent risk of the drug manufactured, prepared, propagated, compounded, or processed at the establishment and other factors. 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.

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[15] Refer to FDA guidance for industry *Process Validation: General Principles and Practices* (Rev 1) for a description of other sections of 21 CFR part 211 that set forth requirements related to aspects of process validation.

[16] FDASIA section 711 added text to section 501 of the FD&C Act clarifying that, for the purposes of paragraph 501(a)(2)(B), the term "current good manufacturing practice" includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.

[17] See 21 CFR 211.180(e) and section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)).

[18] Refer to FDA guidance for industry *Process Validation: General Principles and Practices* (Rev 1).

[19] The Product Quality Review of APIs is comparable to the Annual Product Review conducted for finished drug products under 21 CFR 211.180(e). Refer to FDA guidance for industry *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients.*

III. REPORTING OF QUALITY DATA AND CALCULATION OF QUALITY METRICS

A. Who Reports and Who May Contribute to a Report

1. Covered Establishments and Covered Drug Products

Except as noted below, owners and operators of each establishment that is engaged in the manufacture, preparation, propagation, compounding, or processing of a covered drug product, or an API used in the manufacture of a covered drug product, may submit quality metrics data. For purposes of this guidance, we will refer to the types of establishments whose owners or operators directly or indirectly submit reports as "covered establishments."

For purposes of reporting a covered drug product or an API used in the manufacture of a covered drug product, a covered drug product is:

- subject to an approved application under section 505 of the FD&C Act or under section 351 of the Public Health Service Act (PHS) Act,
- marketed pursuant to an OTC monograph, or
- a marketed unapproved finished drug product.

Covered establishments also include (but are not limited to) contract laboratories, contract sterilizers, contract packagers,[20] 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.

2. Who Reports for Covered Establishments

This guidance describes two types of quality metric data reports: (1) product reports submitted by product reporting establishments,[21] and (2) site reports submitted by site reporting establishments. We encourage reports from product reporting establishments and site reporting establishments. 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.

[20] Contract re-packagers that purchase product and repackage it into a different *primary packaging* configuration are included (e.g., large bottles of tablets repackaged into unit dose blister packs). Contract re-packagers that purchase product and repackage into secondary or tertiary packaging are not included.

[21] A "product reporting establishment" is one establishment who will already possess or have access to all of the quality metrics data needed to submit such reports. It is further defined in section III.A.2.a.

Compilation of data into a single product report will facilitate data analysis and identification of product specific issues (e.g., potential loss in drug supply).

a. Submission of a product report by a product reporting establishment

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 report may include quality metrics data from each covered establishment within the manufacturing supply chain that has the data described in this guidance. 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 — for example, through contract or because all of the covered establishments with quality metrics data related to a covered drug product or API used in the manufacture of a covered drug product will be under common ownership or control.[22] 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 manufacturers often use multiple API suppliers.

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.[23]

FDA believes that the quality control unit (QCU)[24] in each reporting establishment for a covered drug product or API used in a covered drug product will generally be best positioned to compile reports for submission to FDA, considering the QCU responsibilities and authorities for the oversight of drugs as described in 21 CFR 211.22.[25]

b. 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."

[22] See, e.g., FDASIA section 711; 21 CFR 200.10(b).
[23] Refer to Appendix A.1, A.2, A.3, and A.4.
[24] For the purpose of this guidance, the term "quality control unit" is synonymous with "quality unit."
[25] For APIs, these responsibilities are described in FDA guidance for industry *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (section 2.2).

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.[26]

B. Quality Metrics that FDA Intends to Calculate

The following set of quality metrics that FDA intends to calculate based on industry reporting was developed with stakeholder input. 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 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. FDA believes that these quality metrics data, in conjunction with other data accessible to FDA, provide important information about operational reliability.

Using reported data described in the following section, FDA intends to calculate quality metrics for each product and covered establishment, where applicable:

- **Lot Acceptance Rate (LAR)** as an indicator of manufacturing process performance. LAR = the number of accepted lots in a timeframe divided by the number of lots started by the same covered establishment 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 distributed in the current reporting timeframe.

- **Invalidated Out-of-Specification (OOS) Rate (IOOSR)** as an indicator of the operation of a laboratory. IOOSR = the number of OOS test results for lot release[27] and long-term stability testing invalidated by the covered establishment due to an aberration of the measurement process divided by the total number of lot release and long-term stability OOS test results in the current reporting timeframe.[28,29]

C. Quality Metrics Data that May Be Reported

Section IV.B describes the types of metrics FDA intends to calculate and the associated data that may be submitted to calculate and understand each metric. FDA encourages product reporting establishments to submit product reports, segmented by covered establishment, where possible.[30]

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[26] Refer to Appendix A.5, A.6, A.7, and A.8.
[27] This term does not refer to samples and protocols under 21 CFR 610.2.
[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.
[29] The metric measures invalidated lot release OOS results and long-term stability OOS results, separately.
[30] FDA anticipates that data relevant to contract laboratories will generally be limited to the number of OOS results, the number of lot release and stability tests conducted, and the number of invalidated OOS.

The quality metrics data described in this draft guidance is developed and maintained in the course of manufacturing drugs in compliance with CGMP. In general, the information that FDA will receive is maintained in accordance with 21 CFR 211 subpart J and evaluated under 21 CFR 211.180(e). For non-finished drug products (e.g., APIs), refer to section 501(a)(2)(B) of the FD&C Act and FDA guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*. Data that is summed and reported as described in this section is in a readily accessible format for analysis.

Reporting of data related to lots of drugs that are imported, intended for import into the United States, or manufactured in the United States is preferred. However, 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. Further, lots manufactured outside of the United States may be split after manufacturing is completed and a portion is imported, or intended for import into the United States. In these instances, 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 selection of drugs that are either: (1) imported, intended for import, or manufactured in the United States, or (2) all drugs using the same manufacturing process and controls which are not necessarily imported, intended for import, or manufactured in the United States, should remain consistent within and across reporting cycles, unless otherwise specified. Product quality complaint data should be related to drugs that are imported, intended for import or manufactured in the United States.

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).

(1) Lot Acceptance Rate (LAR) Data:

- The number of saleable lots *started* which are intended for primary packaging or distribution.

- The number of saleable lots *released* for primary packaging or distribution.

- The number of saleable lots started which are intended for primary packaging or distribution and were *rejected.*

- The number of lots *started* of in-process and packaging product lots which are intended for distributed product.

- The number of in-process and packaging product lots *released* which are intended for distributed product.

- The number of in-process and packaging product lots which were intended for distributed product and were *rejected*.

Specific criteria for the LAR data:

- 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.

- A lot may be subdivided or grouped after the first started lot is initiated. Each subsequent subdivision or grouping is considered a separate lot.

- Examples of packaging product lots include multiple packaging configurations of bulk tablets (e.g., small bottles, large bottles, blisters) and labeling filled sterile vials with multiple labels (e.g., intended for different countries). The packaging operation can be stand-alone lots or included in an existing lot.

- 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 (e.g., work in progress, lots evaluated for batch release, lots pending disposition due to quality-related discrepancies). 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 text box to explain the occurrence of such an anomaly.

(2) Invalidated OOS Rate Data (IOOSR):

- 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 lot 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.

- The number of OOS results for lot release tests and long-term stability tests for the finished drug product or API where the source of the OOS result is identified as an aberration of the measurement process and where the stability test supports the labeled expiration date.

Specific criteria for the IOOSR data:

- An investigation must be conducted whenever an OOS result is obtained.[31] 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, and (2) all finished drug product and API and long-term stability test results that initially indicate OOS, even if the source of the OOS is investigated and determined to be an aberration of the measurement process. See FDA guidance for Industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production (October 2006)*, section III, and FDA guidance for industry *Sterile Drugs Products Produced by Aseptic Processing – Current Good Manufacturing Practice (September 2004)*, section XI.

- The 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 the 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).

- 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.

- A test includes a single analytical result for lot release or a stability timepoint with an established limit (e.g., analytical chemistry, release sterility test). For example: (1) for lot release, the final content uniformity result as reported on a Certificate of Analysis is considered one test; (2) for a stability timepoint, each test performed in the timepoint would count as an individual test.

- A covered establishment that manufactures API used in a covered drug product is not expected to report stability OOS results.

- For stability testing, only tests that support real-time stability of the product should be counted (i.e., accelerated stability testing is excluded).

- 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.

- FDA recognizes the importance of other types of testing not discussed in this guidance (e.g., in-process testing, environmental testing, raw material and packaging component testing). However, results of these tests should not be counted in this report.

(3) Product Quality Complaint Rate (PQCR):

- The number of product quality complaints received for the product.

[31] See 21 CFR 211.192 and section 501(a)(2)(B) of the FD&C Act.

- The total number of dosage units distributed for the product.

Specific criteria for the PQCR data:

- The total number of all product quality complaints is based on the definition in the glossary. This number does not include multiple counting of the same product quality complaint if the complaint receiver forwards the complaint to individual manufacturers for further investigation. This number does include all potential quality issues, such as subpotency (e.g., a patient report of lack of effect).

- The total number of dosage units distributed for the product is defined in the glossary.

D. How to Submit Comments Within a Quality Metric Data Report and How to Pose Questions to FDA

Reporting establishments may submit a 300-word text comment to provide an explanation of submitted data or report plans for improvement. FDA may refer to the comments if unusual data or trends are identified, or in preparation for an on-site inspection. The submission of comments is optional. In the future, FDA may consider establishing a set of codes to standardize the comments.

Comments may describe special situations, such as natural disasters, the use of emerging technology, or describe the manufacturing supply chain or a plan for improvement. For example, an unexpected decrease in lot acceptance rate may be due to a situation outside the control of the facility (e.g., an act of nature such as a storm or fire). For emerging technology, the use of new, in-line analytical technology used for real time release testing with increased sensitivity might result in better detection of in-process OOS results used for Real Time Release Testing and thus, a temporary increase in total OOS results. However, improved detection that allows for the diversion and rejection of poor quality product will provide improved assurance of quality. In this instance, it may be appropriate to provide an explanation that new, improved technology was implemented and that there is data demonstrating that more robust product was released to the market as a result of this change (e.g., increased lot uniformity would be appropriate).

Upon gathering this data, any questions that a covered establishment may have about their specific situation can be sent to OPQ-OS-QualityMetrics@fda.hhs.gov.

E. How to Report Quality Metrics Data to FDA

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. Therefore, reporting establishments may submit quality metrics data reports where the

data is segmented on a quarterly basis throughout a single calendar year.[32] 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.

Appendix A of the draft guidance is a quality component list with the information for submission into the electronic portal as well as a description of applicable quality metrics data elements relevant for different business segments/types. The associated Technical Conformance Guide describes additional technical details.[33]

IV. THE USE OF QUALITY METRICS AND PUBLIC REPORTING

A. How FDA Intends to Use Quality Metrics

FDA intends to use data from the quality metrics reporting program to focus the use of FDA resources on the areas of highest risk to public health (e.g., risk-based inspection scheduling). Specifically, we intend to:

- establish a signal detection program as one factor in identifying establishments and products that may pose significant risk to consumers;
- identify situations in which there may be a risk for drug supply disruption;
- improve the effectiveness of establishment inspections; and
- improve FDA's evaluation of drug manufacturing and control operations.

Shortages of drugs can pose a significant public health threat; delaying, and in some cases even denying, critically needed care for patients. Taking action to reduce drug shortages remains a top priority for FDA. The Agency has found that the majority of drug shortages stem from quality concerns—substandard manufacturing facilities or processes are discovered, or significant quality defects are identified in finished drug product, necessitating remediation efforts to fix the issue, which in turn, may interrupt production and cause a drug shortage. 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.

FDA may not be able to accomplish the overall goals of an FDA quality metrics reporting program, as described in this draft guidance, from voluntary reporting alone. If FDA does not receive a large body of data from reporting establishments, the ways in which the Agency can use the information may be limited. For example, data received may not constitute a representative sample of the industry. Further, a self-selection bias may increase the risk of signaling an outlier where none exists. For these reasons, we expect to use the information collected to specifically focus on: (1) working with establishments towards early resolution of

[32] More details about the timing of the program are in the notice announcing the availability of this draft guidance in the *Federal Register*.
[33] See http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/UCM508464.pdf.

potential quality problems and to reduce the likelihood that the establishment's operations will be disrupted and impact the drug supply, (2) helping to prepare for and direct our inspections, and (3) using the calculated metrics as an element of the post-approval manufacturing change reporting program with an emphasis on encouraging lifecycle manufacturing improvement.

While FDA recognizes the value of quality metrics, we also recognize that the individual data points and metrics described in this guidance, either individually or in combination, do not definitively quantitate the quality of the establishment or its products. Further, FDA continues to encourage the adoption of emerging technology. We request comments on implementing new technology while maintaining robust quality metrics programs.

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.

B. Quality Metric Reporters List

FDA intends to publish a list of the names of establishments that voluntarily report all or a subset of quality data as described in this guidance (i.e., product reporting establishments and site reporting establishments). We believe that there is a benefit to publicly sharing the names of establishments that voluntarily choose to submit these quality data to FDA because, through their participation, these establishments demonstrate a willingness to proactively engage with the Agency in pursuit of the goals described in this guidance. Participation in this voluntary reporting phase of the program also demonstrates a commitment to increasing transparency between industry and FDA and a contribution to improving quality monitoring throughout the industry.

This list may be useful to establishments within the pharmaceutical manufacturing industry when selecting contract manufacturers and component suppliers as one element of robust outsourcer or supplier selection (e.g., past inspection and regulatory authority history, audits of the facility and associated systems, and analytical testing). This list may also be useful for healthcare purchasing organizations, healthcare providers, patients, and consumers in sourcing drugs when used in conjunction with other information (e.g., inspection history). 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. It should be noted that inclusion on the list is not an indication of FDA's *evaluation* of the submitted data.

The Agency will identify participating establishments on FDA's Web Site according to the following recognition categories:

- For Product Reporting Establishments (finished drug product reporter or API reporter):

- Product Reporter Top Tier: If complete data supporting all metrics were included for each covered establishment in the manufacturing supply chain for all covered drug products (or APIs used in the manufacture of a covered drug product) for the full year reporting period

- Product Reporter Mid Tier: If all covered establishments in the manufacturing supply chain for all covered products were identified in the report, and complete quality metric data was provided from at least one of the establishments for each covered drug products (or APIs used in the manufacture of a covered drug product) for the full year reporting period

- Product Supply Chain Reporter:[34] If all covered establishments in the manufacturing supply chain for all covered drug products (or APIs used in the manufacture of a covered drug product) were identified in the report

- For Site Reporting Establishments (finished drug product reporter or API reporter):[35]

  - Site Reporter Top Tier: If complete data supporting all metrics were included for all covered drug products (or APIs used in the manufacture of a covered drug product) for the full year reporting period

  - Site Reporter Mid Tier: If complete data supporting all metrics were included for at least one covered drug product (or API used in the manufacture of a covered drug product) manufactured at an establishment for the full year reporting period

For example, if product reporting establishment Company ABC submitted a report identifying all covered establishments in the manufacturing supply chain for all covered drug products (or APIs used in the manufacture of a covered drug product), but did not provide quality metrics data, Company ABC would have a "Product Supply Chain Reporter" designation. If product reporting establishment Company ABC submitted a report identifying all establishments in the manufacturing supply chain for all covered drug products (or APIs used in the manufacture of a covered drug product), and metrics data was provided from the primary manufacturing establishment for each product or API, but incomplete data was submitted from the other establishments in the manufacturing supply chain, Company ABC would have a "Product Reporter Mid Tier" designation. If product reporting establishment Company ABC submitted a complete report for the data listed above for all covered drug products (or APIs used in the manufacture of a covered drug product), Company ABC would have a "Product Reporter Top Tier" designation.

[34] "Product Supply Chain Reporter" is defined for the purpose of FDA's quality metric reporting program and is not associated with Title II of the Drug Quality and Security Act, the Drug Supply Chain Security Act (DSCSA).
[35] An establishment may be considered a site reporting establishment by either: (1) directly submitting data to FDA (not applicable for product reporting establishments), or (2) indirectly submitting data to FDA via a product report, submitted by a product reporting establishment.

For site reporters, if contract manufacturer Company XYZ manufactures 30 covered drug products and submitted a report with at least one covered drug product produced at the establishment and data supporting all metrics, Company XYZ would have a "Site Reporter Mid Tier" designation. If the report contains data for all 30 products and all metrics for each covered drug product, Company XYZ would have a "Site Reporter Top Tier" designation. Alternatively, if Company XYZ submitted data to reporting establishments and the data covers each product manufactured at the site, and the submitted product reports reference this establishment, Company XYZ would also have a "Site Reporter Top Tier" designation.

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.

GLOSSARY

Active Pharmaceutical Ingredient (API)[36] – any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body. Active pharmaceutical ingredient does not include intermediates used in the synthesis of the substance. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

Batch – a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.[37] A batch may be comprised of one lot or multiple lots.

Continued Process Verification – A process validation activity where ongoing assurance is gained during routine production that the process remains in a state of control.[38]

Critical Quality Attribute (CQA) – A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.[39]

Dosage Units – the total number of individual dosage units (e.g., 100,000 tablets, 50,000 vials, 50 kg), distributed or shipped under the approved application or product family (for non-application products) to customers, including distributors.[40]

Establishment – a place of business under one management at one general physical location. The term includes, among others, independent laboratories that engage in control activities for a registered drug establishment (e.g., consulting laboratories).[41]

Finished Dosage Form (FDF) – the physical manifestation of a drug product that contains the active ingredient(s) and/or inactive ingredients that are intended to be delivered to the patient. Examples include tablets, capsules, vials, solutions, creams, or ointments.[42]

Finished Drug Product – a finished dosage form (FDF) (e.g., tablet, capsule, or solution) that contains at least one active pharmaceutical ingredient, generally, but not necessarily, in association with other ingredients in finished package form suitable for distribution to

[36] Refer to 21 CFR 207.1 (effective November 29, 2016) and 21 CFR 210.3(b)(7).
[37] See 21 CFR 210.3(b)(2).
[38] Refer to FDA guidance for industry *Process Validation: General Principles and Practices* (Rev 1).
[39] Refer to FDA guidance for industry *Q8(R2) Pharmaceutical Development*.
[40] See 21 CFR 314.81(b)(2)(ii)(a), 211.196.
[41] See 21 CFR 207.1 (effective November 29, 2016).
[42] Refer to "dose form" as defined in ISO 11616:2012(en), *Health informatics – Identification of medicinal products – Data elements and structures for the unique identification and exchange of regulated pharmaceutical product information*.

pharmacies, hospitals, or other sellers or dispensers of the drug product to patients or consumers.[43]

Long-term testing – Stability studies under the recommended storage condition for the retest period or shelf life proposed (or approved) for labeling.[44]

Lot – a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.[45]

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 root cause and the associated investigation supports the release of the lot, it should be considered an accepted lot.[46] Investigations into low yield results should be thorough and managed by the quality unit. 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. 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.

Started Lot – a lot intended for commercial use for which the manufacturer has issued a lot number, physically charged API (for finished drug manufacturers) or primary starting materials (for API manufacturers), and there will be a disposition decision.[47] 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. If unique lot numbers are issued for different packaging configurations, each lot number should be counted.

[43] See 21 CFR 207.1 (effective November 29, 2016).
[44] See FDA guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*.
[45] See 21 CFR 210.3(b)(10).
[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, (2) if an API lot is reworked and released under the original lot number, the lot is considered an accepted lot, (3) for continuous manufacturing, if there was an unplanned shut down of the line due to quality reasons, this would be not be considered an accepted lot, (4) if the entire lot is rejected due to an OOS, the lot would not be considered an accepted lot, and (5) if the entire lot is rejected due to a potential contamination, the lot would not be an accepted lot.
[47] See 21 CFR 211.101.

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).[48,49]

Out-of-Specification (OOS) Result – all test results that fall outside the specifications or acceptance criteria established in drug applications, drug master file, official compendia, or by the manufacturer.[50] An investigation must be conducted whenever an OOS result is obtained.[51] 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]

> **Invalidated OOS** – any out-of-specification result where the investigation identifies the source of the OOS result as an aberration of the measurement process. Invalidation of a discrete test result may be done only upon the observation and documentation of a test event that can reasonably be determined to have caused the OOS result.[54] For the purpose of the quality metrics program, the following test events should be included: (1) lot release[55] and stability test results *only* and, (2) all lot release and stability test results that initially appear as OOS, even if invalidated by a subsequent laboratory investigation.

Periodic Product Review – an evaluation, conducted at least annually, of the quality standards of a drug product to determine the need for changes in drug product specifications or manufacturing or control procedures.[56]

Product Family – for finished drug products, any combination of National Drug Code (NDC) product code segments where the API and FDF is the same (i.e., a product family could be multiple strengths or only a single strength).[57] For APIs, the product family is defined by the NDC product code segment. A product family is defined for the purpose of grouping non-application drugs for the submission of quality metric data. Grouping is likely consistent with how products are grouped for the Periodic Product Review (e.g., Annual Product Review).[58]

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[48] See 21 CFR 211.165.
[49] This term does not refer to samples and protocols under 21 CFR 610.2.
[50] See FDA guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*.
[51] See 21 CFR 211.192 and section 501(a)(2)(B) of the FD&C Act.
[52] For example, if a near infrared (NIR) spectroscopy-based method is approved for testing active content of core tablets for release as an alternative to testing active content on finished tablets by traditional high-performance liquid chromatography (HPLC) method, and the NIR result is reported on the Certificate of Analysis, this test should be counted as a single analytical result and OOS result, as appropriate, for the purpose of this guidance.
[53] Each test may also be defined as a single analytical result listed on the Certificate of Analysis.
[54] See 21 CFR 211.160(a) and FDA guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*.
[55] This term does not refer to samples and protocols under 21 CFR 610.2.
[56] See 21 CFR 211.180(e).
[57] See 21 CFR 207.35.
[58] See 21 CFR 211.180(e).

643
644 **Product Quality Complaint** – a complaint involving any possible, including actual, failure of a
645 drug to meet any of its specifications designed to ensure that any drug conforms to appropriate
646 standards of identity strength, quality, and purity.[59]

[59] See, e.g., 21 CFR 211.160(b); 211.198.

APPENDIX A: APPLICABLE IDENTIFYING INFORMATION AND QUALITY METRIC DATA ELEMENTS FOR PRODUCT REPORTS AND SITE REPORTS

This appendix provides clarity on which identifying information and quality metric data elements are applicable for submission in the voluntary phase of the quality metrics reporting program. Technical details of quality metric data submissions are provided in the Technical Conformance Guide.[60] Data standards are available for certain identifying information elements (e.g., dose forms, business operations).[61]

Appendix A is separated into eight (8) subparts. Each subpart corresponds to a different combination of report type, establishment type, and product type, as described in this draft guidance. Specifically:

- Product Report, segmented by all sites[62]
  - Application Product
    - Finished Drug Product: Appendix A.1
    - API: Appendix A.2
  - Non-Application Product
    - Finished Drug Product: Appendix A.3
    - API: Appendix A.4

- Site Report, segmented by products
  - Manufacturing with product quality oversight responsibilities only: Appendix A.5
  - Manufacturer with testing responsibilities: Appendix A.6
  - Manufacturer without testing responsibilities: Appendix A.7
  - Manufacturer with testing responsibilities only: Appendix A.8

[60] See http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/UCM508464.pdf.
[61] See http://www.fda.gov/forindustry/datastandards/structuredproductlabeling/ucm162038.htm.
[62] For a product report, when information was not provided by a contract facility, the corresponding data elements should be marked as "not provided."

673 *Appendix A.1: Applicable Inputs for a Product Report Submission, Application Product, Finished Drug Product*
674

	Product Name	Rx/OTC	OTC Monograph	Product Type	Applicant Name	Application Type	Application Number	NDC Product Code Number(s)	Reporting Time Period	Quarter	Dose Form	Active Ingredient	Supply Chain/Process Stage Code	FEI/DUN	Started: In-process/Packaging	Started: Saleable	Rejected: In-process/Packaging	Rejected: Saleable	Released: In-process/Packaging	Released: Saleable	Number of quality complaints	Number of Dosage Units Distributed	Sum of Release test and Stability test OOS results where the source of the OOS result is identified as an aberration of the measurement process	Sum of Release test and Stability test OOS results	Sum of all Release and Stability Tests
Product Reporting Establishment [Manufacturing with oversight responsibilities only]	X	X	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	N/A
Contract Manufacturer performing release or stability testing	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X
Contract Manufacturer not performing release or stability testing (FDF, packaging, sterilizing, etc.)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	X	X	X	X	X	X	X	X	N/A	N/A	N/A
Contract Laboratory performing release or stability testing only	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	X

675 X = Input is applicable to report; N/A = Input is not applicable to report

676 *Appendix A.2: Applicable Inputs for a Product Report Submission, Application Product, API*
677

	Product Name	Rx/OTC	OTC Monograph	Product Type	Applicant Name	Application Type	Application Number	NDC Product Code Number(s)	Reporting Time Period	Quarter	Dose Form	Active Ingredient	Supply Chain/Process Stage Code	FEI/DUN	Started: In-process/Packaging	Started: Saleable	Rejected: In-process/Packaging	Rejected: Saleable	Released: In-process/Packaging	Released: Saleable	Number of quality complaints	Number of Dosage Units Distributed	Sum of Release test and Stability test OOS results where the source of the OOS result is identified as an aberration of the measurement process	Sum of Release test and Stability test OOS results	Sum of all Release and Stability Tests
Product Reporting Establishment [Manufacturing with oversight responsibilities only]	X	N/A	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	N/A
Contract Manufacturer performing release or stability testing	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X
Contract Manufacturer not performing release or stability testing (FDF, packaging, sterilizing, etc.)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	X	X	X	X	X	X	X	X	N/A	N/A	N/A
Contract Laboratory performing release or stability testing only	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	X

678 X = Input is applicable to report; N/A = Input is not applicable to report

679 *Appendix A.3: Applicable Inputs for a Product Report Submission, Non-application Product, Finished Drug Product*
680

	Product Name	Rx/OTC	OTC Monograph	Product Type	Applicant Name	Application Type	Application Number	NDC Product Code Number(s)	Reporting Time Period	Quarter	Dose Form	Active Ingredient	Supply Chain/Process Stage Code	FEI/DUN	Started: In-process/Packaging	Started: Saleable	Rejected: In-process/Packaging	Rejected: Saleable	Released: In-process/Packaging	Released: Saleable	Number of quality complaints	Number of Dosage Units Distributed	Sum of Release test and Stability test OOS results where the source of the OOS result is identified as an aberration of the measurement process	Sum of Release test and Stability test OOS results	Sum of all Release and Stability Tests
Product Reporting Establishment [Manufacturing with oversight responsibilities only]	X	X	X	X	N/A	N/A	N/A	X	X	X	X	X	X	X	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	N/A
Contract Manufacturer performing release or stability testing	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X
Contract Manufacturer not performing release or stability testing (FDF, packaging, sterilizing, etc.)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	X	X	X	X	X	X	X	X	N/A	N/A	N/A
Contract Laboratory performing release or stability testing only	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	X

681 X = Input is applicable to report; N/A = Input is not applicable to report

682 *Appendix A.4: Applicable Inputs for a Product Report Submission, Non-application Product, API*
683

	Product Name	Rx/OTC	OTC Monograph	Product Type	Applicant Name	Application Type	Application Number	NDC Product Code Number(s)	Reporting Time Period	Quarter	Dose Form	Active Ingredient	Supply Chain/Process Stage Code	FEI/DUN	Started: In-process/Packaging	Started: Saleable	Rejected: In-process/Packaging	Rejected: Saleable	Released: In-process/Packaging	Released: Saleable	Number of quality complaints	Number of Dosage Units Distributed	Sum of Release test and Stability test OOS results where the source of the OOS result is identified as an aberration of the measurement process	Sum of Release test and Stability test OOS results	Sum of all Release and Stability Tests
Product Reporting Establishment [Manufacturing with oversight responsibilities only]	X	X	X	X	N/A	N/A	N/A	X	X	X	X	X	X	X	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	N/A
Contract Manufacturer performing release or stability testing	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X
Contract Manufacturer not performing release or stability testing (FDF, packaging, sterilizing, etc.)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	X	X	X	X	X	X	X	X	N/A	N/A	N/A
Contract Laboratory performing release or stability testing only	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	X

684 X = Input is applicable to report; N/A = Input is not applicable to report

Appendix A.5: Applicable Inputs for a Site Report Submission, Manufacturer with oversight responsibilities only (e.g., application holder)

	Product Name	Rx/OTC	OTC Monograph	Product Type	Applicant Name	Application Type	Application Number	NDC Product Code Number(s)	Reporting Time Period	Quarter	Dose Form	Active Ingredient	Supply Chain/Process Stage Code	FEI/DUN	Started: In-process/Packaging	Started: Saleable	Rejected: In-process/ Packaging	Rejected: Saleable	Released: In-process/Packaging	Released: Saleable	Number of quality complaints	Number of Dosage Units Distributed	Sum of Release test and Stability test OOS results where the source of the OOS result is identified as an aberration of the measurement process	Sum of Release test and Stability test OOS results	Sum of all Release and Stability Tests
Finished Drug Product – Application	X	X	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	N/A
Finished Drug Product – Non-application	X	X	X	X	N/A	N/A	N/A	X	X	X	X	X	X	X	X	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	N/A
API – Application	X	N/A	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	X	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	N/A
API – Non Application	X	N/A	X	X	N/A	N/A	N/A	X	X	X	X	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	N/A

X = Input is applicable to report; N/A = Input is not applicable to report

Appendix A.6: Applicable Inputs for a Site Report Submission, Manufacturer that perform testing

	Product Name	Rx/OTC	OTC Monograph	Product Type	Applicant Name	Application Type	Application Number	NDC Product Code Number(s)	Reporting Time Period	Quarter	Dose Form	Active Ingredient	Supply Chain/Process Stage Code	FEI/DUN	Started: In-process/Packaging	Started: Saleable	Rejected: In-process/Packaging	Rejected: Saleable	Released: In-process/Packaging	Released: Saleable	Number of quality complaints	Number of Dosage Units Distributed	Sum of Release test and Stability test OOS results where the source of the OOS result is identified as an aberration of the measurement process	Sum of Release test and Stability test OOS results	Sum of all Release and Stability Tests
Finished Drug Product – Application	X	X	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X
Finished Drug Product– Non-application	X	X	X	X	N/A	N/A	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
API – Application	X	N/A	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X
API – Non Application	X	N/A	X	X	N/A	N/A	N/A	X	X	X	X	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X

X = Input is applicable to report; N/A = Input is not applicable to report

Appendix A.7: Applicable Inputs for a Site Report Submission, Manufacturer that does not perform testing

	Product Name	Rx/OTC	OTC Monograph	Product Type	Applicant Name	Application Type	Application Number	NDC Product Code Number(s)	Reporting Time Period	Quarter	Dose Form	Active Ingredient	Supply Chain/Process Stage Code	FEI/DUN	Started: In-process/Packaging	Started: Saleable	Rejected: In-process/Packaging	Rejected: Saleable	Released: In-process/Packaging	Released: Saleable	Number of quality complaints	Number of Dosage Units Distributed	Sum of Release test and Stability test OOS results where the source of the OOS result is identified as an aberration of the measurement process	Sum of Release test and Stability test OOS results	Sum of all Release and Stability Tests
Finished Drug Product–Application	X	X	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	X	X	X	X	X	X	X	X	N/A	N/A	N/A
Finished Drug Product–Non-application	X	X	X	X	N/A	N/A	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	N/A	N/A
API – Application	X	N/A	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	X	X	X	X	X	X	X	X	N/A	N/A	N/A
API – Non Application	X	N/A	X	X	N/A	N/A	N/A	X	X	X	X	N/A	X	X	X	X	X	X	X	X	X	X	N/A	N/A	N/A

X = Input is applicable to report; N/A = Input is not applicable to report

Appendix A.8: Applicable Inputs for a Site Report Submission, Manufacturer with Testing Only

`	Product Name	Rx/OTC	OTC Monograph	Product Type	Applicant Name	Application Type	Application Number	NDC Product Code Number(s)	Reporting Time Period	Quarter	Dose Form	Active Ingredient	Supply Chain/Process Stage Code	FEI/DUN	Started: In-process/Packaging	Started: Saleable	Rejected: In-process/Packaging	Rejected: Saleable	Released: In-process/Packaging	Released: Saleable	Number of quality complaints	Number of Dosage Units Distributed	Sum of Release test and Stability test OOS results where the source of the OOS result is identified as an aberration of the measurement process	Sum of Release test and Stability test OOS results	Sum of all Release and Stability Tests
Finished Drug Products– Application	X	X	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	X
Finished Drug Product – Non-application	X	X	X	X	N/A	N/A	N/A	X	X	X	X	X	X	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	X
API – Application	X	N/A	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	X
API – Non Application	X	N/A	X	X	N/A	N/A	N/A	X	X	X	X	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	X

X = Input is applicable to report; N/A = Input is not applicable to report

APPENDIX B: EXAMPLES

(1) Lot Acceptance Rate

a. An establishment manufactures a product where six small in-process lots are combined into a single unit operation to make one saleable lot (e.g., tablet, liquid, filled vial). Two saleable lots are then combined into one packaging lot.

Assuming all lots that are started are released:

- In-process and packaging lots started and released: 13 [six lots from the first saleable lot, six lots from the second saleable lot, and the single packaging lot]
- Saleable lots started and released: 2

b. An establishment manufactures one saleable lot that is separated into five packaged lots.

Assuming all lots that are started are released:

- In-process and packaging lots started and released: 5
- Saleable lots started and released: 1

c. 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.

d. 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.

e. For a non-functional or functional film-coated tablet where the coating process consists of multiple separate coating pan loads, 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. For either functional or non-functional coatings, samples collected and testing for finished drug product release should be representative of the lot.

f. 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.

(2) Product Quality Complaint Rate

a. If a lot is distributed to five customers and all customers report the same complaint, this should be counted as five complaints.

b. 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.

c. A lot is distributed to three regions and a complaint is received on that lot from a region outside of the United States. In this instance, the complaint does not need to be reported as part of the quality metrics program. The covered establishment may choose to include this complaint if it could be applicable to product imported or intended for import to the United States or its territories.

d. 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.

(3) Invalidated Out of Specification (OOS) Result Rate

a. Regarding analytical tests with multiple sample preparations or injections involved in the test to generate the final result, one test is represented by a single analytical result with an established limit. For example, one content uniformity test proceeding to stage two may have 30 invalidated results. Only one OOS result would be counted.

b. If two samples from one lot are tested with two injections each and there is one result reported on the Certificate of Analysis, this is considered one release test.

c. If an OOS result occurs during in-process testing for a test that is considered a real time release test, this is considered a release OOS result for the purpose of this guidance.

d. If more than one OOS result is observed during finished drug product testing (e.g., the lot fails both assay and uniformity), this is considered multiple release OOS results.

e. 50 kg of an API is packaged into five 10 kg packages and three to five of the five containers are tested; the Certificate of Analysis reports the average. If one or more of the container results is OOS for the same attribute, the establishment should initiate an OOS investigation and count these OOS results as a single OOS result. A single API container with an OOS result should result in an investigation for the lot in its entirety. After the investigation is complete, subsequent retesting should be counted as a new release test.

f. Company A does not declare an OOS result until the laboratory investigation proves the result is valid.[63] If invalid, and the original result is not labeled as an OOS, there will be no record of invalidating an OOS result, thus resulting in a lower Invalidated OOS Rate for Company A. For the purpose of the quality metrics program, a lot release OOS result should be counted prior to the laboratory investigation, in accordance with the term "OOS result" as defined in this guidance. Furthermore, these type of results should be evaluated as part of the PPR to determine the need for changes in drug product specifications or manufacturing or control procedures.[64]

[63] It should be noted that this practice is inconsistent with the recommendations outlined in FDA guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production.*

[64] Refer to 21 CFR 211.180(e).