ACRP Regulatory Affairs Committee Review of FDA Draft Guidance

Request for Quality Metrics

What is the guidance?
This guidance speaks to the Center for Drug Evaluation and Research's (CDER) and the Center for Biologics Evaluation and Research's (CBER) collection and use of quality metrics used by pharmaceutical drug manufacturers to aid the Agency in developing compliance and inspection policies and practices; predicting and mitigating drug shortages; and encouraging pharmaceutical manufacturers to implement state-of-the-art quality systems.

Who does it impact & how?
This primarily impacts owners and operators of establishments involved in the manufacture, preparation, propagation or processing of human drugs.

What did ACRP RAC have to say about it?
ACRP requests clarification from the Agency on the scope of the draft guidance document and possible implications on clinical trial supply manufacture and also questions whether the FDA intends to continue to offer safe harbor for companies attempting to learn about and improve their quality systems.

When were the RAC's comments sent to the agency?
September 22, 2015

Where can I access this document?
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM455957.pdf

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September 22, 2015

Division of Documents Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
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In reference to docket number: **FDA-2015-D-2537-0001**

The Association of Clinical Research Professionals (ACRP) is the primary resource for clinical research professionals in the pharmaceutical, biotechnology and medical device industries, and those in hospital, academic medical center and physician office settings. ACRP was founded in 1976 to address the educational and networking needs of research nurses and others who supported the work of clinical investigations. Almost 40 years later, ACRP is a global association comprised of individuals dedicated to clinical research and development. Our mission is "ACRP promotes excellence in clinical research." The Academy of Physicians in Clinical Research (APCR) is an affiliate of ACRP and is the leading professional organization, exclusive to physicians, that supports and addresses these unique issues and challenges of all physicians involved in clinical research.

ACRP appreciates the opportunity to provide the FDA with our comments on the Request for Quality Metrics draft guidance as this issue has a significant impact on our membership. The FDA is to be commended for seeking improved ways to further minimize drug shortages due to quality issues throughout the supply chain by proactively collecting and analyzing quality metrics that may identify potential breakdowns so that corrective and preventive actions may be quickly implemented by all relevant parties.

The draft guidance states "FDA intends to request the submission of data from owners and operators of certain human drug establishments that are subject to inspection under section 704 of the 48 FD&C Act... The requests would not apply to: establishments that are not required to register under section 510 of the FD&C Act and regulations FDA has issued at 21 CFR 207.10; compounders operating under section 503A or registered as outsourcing facilities under section 503B of the FD&C Act; medical gas manufacturers; positron emission tomography manufacturers; and manufacturers of blood and blood components for transfusion, vaccines, cell therapy products, gene therapy products, allergenic extracts, human cells, tissues, and cellular and tissue based products and non-recombinant versions of plasma derived products."

ACRP is a global association comprised of individuals dedicated to clinical research and development. As such, our primary concerns for our research subjects are three-fold:

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1. to ensure that investigational products undergoing clinical trials meet appropriate quality standards for such investigational products
2. continuity of supply of these investigational products is not unduly placed at risk by overly onerous GMP requirements, especially in early clinical testing
3. alternative mechanisms are in place to ensure that establishments that are exempted from requests for quality metrics as described have adequate quality systems in place manufacture clinical trial supplies of all kinds, and that these establishments have sufficient supply capacity to meet clinical trial commitments as set out in IND or other applicable documents for any approved clinical trials under an IND.

ACRP would therefore welcome further clarification in the draft guidance firstly to clarify whether drugs manufactured and distributed for investigational use are covered by this draft guidance and if so, we request further details regarding possible implications to clinical trial supply manufacture, particularly in view of the difficulties inherent in controlling complex processes used to manufacture products of biologic origin.

In addition, this draft guidance prompts ACRP to wonder if FDA intends to continue to offer safe harbor for companies attempting to learn about and improve their quality systems, or has the concept of an internal, open, quality review free from FDA scrutiny becoming obsolete with the introduction of these new types of expanding FDA expectations (i.e., draft guidelines) into areas where no such expectations existed previously?

We hope that our feedback helps improve the final version of the document. Please let me know if you have any questions regarding our comments, or if we may otherwise serve as a resource on issues related to clinical research.

Sincerely,

Terri Hinkley, RN, BScN, MBA, CCRC
Interim Executive Director

Request for Quality Metrics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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 240-402-7800.

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)

July 2015
Pharmaceutical Quality/CMC
Current Good Manufacturing Practices (CGMPs)

Request for Quality Metrics

Guidance for Industry

Additional copies are available from:
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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)

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Pharmaceutical Quality/CMC
Current Good Manufacturing Practices (CGMPs)

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Request for Quality Metrics 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 pharmaceutical industry to monitor quality control systems and processes and drive continuous improvement efforts in drug manufacturing. These metrics can also be used by 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 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 collect data and use quality metrics to help ensure that their policies and practices continue to support continuous improvement and innovation in the pharmaceutical manufacturing industry.

FDA understands that establishments involved in the manufacture, preparation, propagation, or processing of human drugs, including oversight to ensure quality,[2] currently use quality metrics as part of the process validation lifecycle and pharmaceutical quality system (PQS) assessment.[3] This guidance outlines FDA's authority to require owners and operators of such establishments to provide upon request records and information that FDA may inspect under section 704 of the Federal Food, Drug, and Cosmetic Act (FD&C Act, or the Act), and describes an initial set of requests the Agency intends to make to certain owners and operators. FDA intends to make its requests at the time this guidance is finalized, and to provide notice in the *Federal Register*. In order to receive public comment on these requests, this draft guidance describes the data that the

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

Agency plans to request, the uses FDA intends to make of the requested data, and the quality metrics that FDA intends to calculate.

Under Title VII 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.[4,5]

Under this authority, FDA intends to request the submission of data from owners and operators of certain human drug establishments that are subject to inspection under section 704 of the FD&C Act. Except as noted below, FDA intends to request data from owners and operators of establishments that are required to register under section 510 of the FD&C Act and that are 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. Covered drug products would include: drug products that are the subject of an approved application under section 505 of the FD&C Act or under section 351 of the PHS Act; products that can be marketed pursuant to an over-the-counter (OTC) monograph; and marketed unapproved drug products.

The requests would not apply to: establishments that are not required to register under section 510 of the FD&C Act and regulations FDA has issued at 21 CFR 207.10; compounders operating under section 503A or registered as outsourcing facilities under section 503B of the FD&C Act; medical gas manufacturers; positron emission tomography manufacturers; and manufacturers of blood and blood components for transfusion, vaccines, cell therapy products, gene therapy products, allergenic extracts, human cells, tissues, and cellular and tissue based products and non-recombinant versions of plasma derived products. Additional detail is provided below.

In addition, establishments that receive requests under section 704(a)(4) would be encouraged to submit quality metrics data for certain foreign establishments that are not required to register, as discussed below.

While FDA recognizes the value of quality metrics, we also recognize that individual data points and metrics are not solely indicative of the state of quality of the establishment or products. Rather, FDA intends to use quality metrics data in context with other sources of quality data, as further described in this guidance.

[4] See section 704(a)(4) of the FD&C Act. Such records or other information must, upon the request of FDA, be provided to FDA within a reasonable timeframe, within reasonable limits, and in a reasonable manner, and in either electronic or physical form, at the expense of such person. Any request shall include a sufficient description of the records requested. Upon receipt of the records requested, FDA must provide confirmation of receipt.

[5] See also sections 262(c) and (j) of the Public Health Service Act (PHS) that authorize inspections for biologics and incorporate FD&C Act requirements by reference. See also sections 351(c) of the PHS Act (authorizing inspections for biologics) and section 351(j) of the PHS Act (providing that the FD&C Act applies to biological products, except that NDAs are not required for biologics approved under BLAs).

FDA intends to carefully review data submitted in response to its requests, to help inform decisions about how to develop its program. FDA may add to, revise, or remove quality metrics data from future quality metrics data requests to reflect our understanding of current manufacturing and establishment considerations and the utility of the data the Agency has received.

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. These efforts also may be one long-term strategy to mitigate drug shortages by addressing underlying causes of shortages, as noted in *FDA's Strategic Plan for Preventing and Mitigating Drug Shortages*.[6] 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 system.[7] The initiative was published with several goals, including ensuring that regulatory review, compliance, and inspection policies continue to 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."[8]

FDA used the following criteria to select the quality metrics that it intends to calculate using requested data when this guidance is final: metrics should be (1) objective, (2) subject to inspection under section 704 of the FD&C Act, and (3) valuable in assessing the overall state of quality of the product and process, commitment to quality by the manufacturer, and the health (i.e., effective functioning) of the associated PQS, while (4) avoiding any undue reporting burden. These metrics are not intended to be an all-inclusive set of the quality metrics that FDA could consider useful to assess a product and manufacturer's state of quality. For example, senior management commitment to quality is an important factor in evaluating the overall health of the PQS and quality culture. While it may be difficult to measure this factor objectively between different companies, the Agency is committed to a dialog with industry to consider

[6] See *FDA's Strategic Plan for Preventing and Mitigating Drug Shortages* at: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf.
[7] See *Pharmaceutical cGMP's for the 21st Century: A Risk-Based Approach* at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm137175.htm.
[8] See *FDA Pharmaceutical Quality Oversight: One Quality Voice* at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM442666.pdf.

benchmarks and standards that could provide acceptable metrics that specifically demonstrate senior management's commitment to a culture of quality (refer to Request for Comment on the Additional Reporting of Optional Metrics - Optional Metrics Related to Quality Culture and Process Capability/Performance, highlighted in section V.B). Also, while FDA has not selected metrics based on data or information that are readily accessible to the Agency, such as number of recalls, these data and information should also be part of manufacturers' product- and establishment-specific evaluations. FDA encourages manufacturers to routinely use additional quality metrics beyond the metrics described in this guidance in performing these evaluations.

B. Use of Quality Metrics by FDA for Risk-Based Inspection Scheduling and Prediction of Drug Shortages

The quality metrics program is expected to play an important role in addressing risk-based inspection scheduling and in the prediction, and potential mitigation, of drug shortages. Section 510(h)(3) of the FD&C Act was amended by section 705 of FDASIA to require that FDA inspect establishments that are required to register with FDA "that are engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs in accordance with a risk-based schedule established by" FDA. The provision replaced the requirement that FDA conduct inspections of certain domestic drug establishments at least once every two years. Risk-based scheduling helps FDA focus resources on facilities that present the greatest risk to consumers.[9]

Section 510(h)(3) of the FD&C Act provides for a risk-based schedule of inspections for drugs be established according to the known safety risks posed by establishments that are required to register. These risks are based on certain factors as outlined in section 510(h)(4)(A-F): (1) the compliance history of the establishment; (2) the record, history, and nature of recalls linked to the establishment; (3) the inherent risk of the drug manufactured, prepared, propagated, compounded, or processed at the establishment; (4) the inspection frequency and history of the establishment, including whether the establishment has been inspected pursuant to section 704 within the last 4 years; (5) whether the establishment has been inspected by a foreign government or agency of a foreign government recognized under section 809 of the FD&C Act; and, (6) any other criteria that FDA deems necessary and appropriate for purposes of allocating inspection resources. FDA intends to use quality metrics to support its understanding of the inherent risk of manufacturing establishments and products and as the basis for criteria it deems necessary and appropriate for purposes of allocating inspection resources.

In addition, shortages of drugs and biologics 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 product, necessitating

[9] See, e.g., U.S. House, Committee on Energy & Commerce, Food and Drug Administration Reform Act of 2012 (H.R. Rep No. 112-495) Washington, Government Printing Office, 31.

remediation efforts to fix the issue, which in turn, may interrupt production, and cause a shortage of drugs.[10]

In order to both inform FDA's risk-based drug inspection scheduling and to better detect manufacturing conditions that may lead to a shortage, FDA intends to collect and use quantitative quality data to calculate certain quality metrics, as further described in section V. FDA intends to use these quality metrics, in part, as a tool to identify risk-based factors that could increase or decrease inspection frequency and that could potentially be predictive of drug supply disruption.

The collection of these data is also intended to help direct our inspections. In addition, FDA intends to consider whether these metrics may provide a basis for FDA to use improved risk-based principles to determine the appropriate reporting category for post-approval manufacturing changes, with emphasis on encouraging lifecycle manufacturing improvement. However, if the integrity or utility of the quality data submitted is found questionable based on FDA's evaluation of submitted data or other information, such as an on-site inspection, the uses to which we would put the reported quality data would need to be re-evaluated, along with the nature of future requests.

III. LEGAL AUTHORITY

A. Records Associated with the Process Validation Lifecycle and PQS Assessment

Manufacturers are expected to use a quality program in order to support process validation, and the metrics described in this guidance could be a part of such a program. Process validation involves a series of activities taking place over the lifecycle of the product and process. Process validation for drugs (finished pharmaceuticals and components) is a requirement under section 501(a)(2)(B) of the Act (21 U.S.C. 351(a)(2)(B)), which states the following:

> A drug . . . shall be deemed to be adulterated . . . if . . . the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

FDA regulations describing current good manufacturing practice (CGMP) requirements for finished pharmaceuticals are provided in 21 CFR parts 210 and 211, including the associated

[10] In 2012, for example, based on information collected from manufacturers, FDA determined that 66 percent of disruptions in drug manufacturing were the result of either (1) efforts to address product-specific quality failures, or (2) broader efforts to remediate or improve an unsafe manufacturing facility. *FDA's Strategic Plan for Preventing and Mitigating Drug Shortages*, see figure 2, at http://www.fda.gov/downloads/drugs/drugsafety/drugshortages/ucm372566.pdf.

record-keeping requirements (21 CFR 211 subpart J). Process validation is required, in both general and specific terms, by the CGMP regulations in parts 210 and 211, for example, 21 CFR 211.100(a) and 211.110(a).[11] 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 that result in products with the desired quality attributes. Manufacturers should:

- Understand the sources of variation.
- Detect the presence and degree of variation.
- Understand the impact of variation on the process and ultimately on product attributes.
- Control the variation in a manner commensurate with the risk it represents to the process and product.

After establishing and confirming the process, manufacturers must 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.[12] Manufacturers should use ongoing programs to collect and analyze product and process information to evaluate the state of control of the process. These programs may identify process or product problems and opportunities for manufacturing improvements that can be evaluated and implemented throughout the lifecycle.

CGMP regulations for human drugs require an ongoing program to maintain and evaluate product and process data that relate to product quality.[13] One means of performing this assessment is the Annual Product Review (APR), which is 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. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process and determine if the specifications, manufacturing, or control procedures should be updated or improved. This evaluation includes a review of a representative number of batches and associated records and complaints, recalls, returned or salvaged drug products, and investigations.[14] Further, maintenance of the facility, utilities, and equipment is another important aspect of ensuring that a process remains in

[11] 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.
[12] 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 an establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.
[13] See 21 CFR 211.180(e).
[14] 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.*

control.[15] The equipment and facility qualification data should be assessed periodically. In order to perform this evaluation, reporting establishments and manufacturers should be calculating and evaluating quality metrics on a continual basis. Some establishments may also choose to adopt systems to internally calculate and evaluate metrics in real time.

B. Authority to Inspect Records and Request Records in Advance of or In Lieu of an Inspection

Section 704(a)(4)(A) of the FD&C Act (added by FDASIA section 706, Records for Inspection) authorizes FDA to request from a person that owns or operates an establishment that is engaged in the manufacture, preparation, propagation, compounding, or processing of a drug, "in advance of or in lieu of" an inspection, any records or other information that we may inspect under section 704 of the FD&C Act, provided we request submission of the information "within a reasonable timeframe, within reasonable limits, and in a reasonable manner." We consider FDA's request for quality metrics data records or information to be "in advance of" an inspection for purposes of section 704(a)(4)(A). FDA intends to request quality data to help FDA improve its inspection-setting priorities, including informing a risk-based inspection schedule to satisfy the requirement in section 510(h) of the FD&C Act. Additionally, FDA intends to use quality metrics data it receives to assist staff in preparing for in-person inspections, to improve their efficiency and effectiveness. Finally, at the Agency's discretion, if quality metrics derived from the data provide evidence of a lower risk of poor quality drugs and an acceptable commitment to high quality drug manufacturing judged in light of other relevant risk information, the requests may reduce the inspection frequency at an establishment.

Under section 501(j) (added by FDASIA section 707), a drug is deemed adulterated if it has been manufactured, processed, packed, or held in a facility the owner of which delays, denies, or limits an inspection, or refuses to permit entry or inspection.[16] If an owner, operator, or agent of a facility fails to produce records and information requested pursuant to section 704(a)(4) of the FD&C Act within a reasonable timeframe, drugs from the facility may be deemed adulterated under section 501 of the Act and subject to enforcement action. Additionally, refusal to permit access to a record as required under section 704(a) of the FD&C Act is a prohibited act under section 301(e) of the Act.

IV. THE USE OF QUALITY METRICS AND EFFECTS OF NON-REPORTING

A. How FDA Intends to Use Quality Metrics

FDA intends to use quality metrics data to further develop FDA's risk-based inspection scheduling, to identify situations in which there may be a risk for drug supply disruption, to improve the efficiency and effectiveness of establishment inspections, and to improve FDA's

[15] See 21 CFR 211 subparts C and D.

[16] For further information regarding 501(j), see FDA guidance for industry *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection*.

evaluation of drug manufacturing and control operations. FDA expects that the initial use of the metrics will be to consider a decreased surveillance inspection frequency for certain establishments. For example, establishments that have highly controlled manufacturing processes have the potential to be inspected less often (as a lower priority for inspection) than similar establishments that demonstrate uncontrolled processes (as a higher priority for inspection). In addition, FDA intends to consider whether these metrics may provide a basis for FDA to use improved risk-based principles to determine the appropriate reporting category for post-approval manufacturing changes.

FDA intends to evaluate whether data reported by manufacturers is consistent with the Agency's understanding of the specific quality data requested (e.g., definitions). In addition, we intend to evaluate how best to interpret and use the metrics. For example, is it more meaningful to compare metrics for different products within the same establishment, or for the same product manufactured at different establishments, or as an establishment-specific trend over time? Is it more appropriate to use certain metrics to compare all types of establishments (or a subset making the same dosage form or same drug) against each other? What is the best way to compare metrics for products that vary in manufacturing complexity (e.g., biotechnology and biological products are often considered more complex to manufacture)?

FDA intends to carefully review data submitted in response to its requests, to help inform decisions about additional quality metrics data requests the Agency may make in the future. We may add to, revise, or remove quality metrics data from future requests to reflect our understanding of current manufacturing and establishment considerations and the utility of the data the Agency has received. We also intend to provide additional opportunity after our initial requests are made for industry to provide feedback and additional comments, as well as share knowledge from ongoing quality metrics programs.

FDA recognizes that any individual data point or quality metric is not solely indicative of the state of quality of the establishment or products; rather, FDA intends to use this information in context. For example, 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 out of specification (OOS) results and a temporary increase in total OOS results. However, improved detection that allows for the diversion and rejection of poor quality product will allow for improved assurance of quality. FDA is sensitive to this possibility and continues to support and encourage the use of modern manufacturing technology.

FDA also intends to use quality data collected under section 704(a)(4)(A) of the FD&C Act as one factor in identifying establishments that may pose significant risks to consumers, such as risks from unsafe products and drug shortages. Reported data and metrics, along with internal FDA data (e.g., inspection results, recalls, Field Alert Reports, Biological Product Deviation Reports) may indicate an ongoing product quality problem that requires correction. Evaluation of this information will enable FDA to work with establishments towards early resolution of quality problems and to reduce the likelihood that the establishment's operations will be disrupted and impact the drug supply. FDA does not intend to publicly disclose quality metric data submissions.

Manufacturers can expect that reported quality data may be verified during on-site inspections. If inconsistencies are identified, the integrity of the report may be questioned and used as an additional factor in FDA risk-based or for-cause inspection scheduling.

B. Effects of Non-Reporting

The failure to report requested quality data may elevate an establishment's predicted risk in FDA's prioritization of inspections and may lead to an earlier inspection. In addition, products associated with an establishment that does not report as required under section 704(a)(4)(A) may be deemed adulterated under section 501 and subject to enforcement action.

V. REPORTING OF QUALITY DATA AND CALCULATION OF QUALITY METRICS

In this section, we describe the set of requests for quality metrics data that FDA intends to make and give notice of in the *Federal Register* at the time the guidance is finalized.

A. Who Reports and Who May Contribute to the Report

As described in section III of this guidance, owners or operators of establishments that are engaged in the manufacture, preparation, propagation, compounding, or processing of a drug are required to report data to FDA that the Agency may inspect under section of the FD&C Act, upon the Agency's request, in advance or in lieu of an inspection. At the time the guidance is finalized, FDA intends to give notice in the *Federal Register* to certain owners and operators of establishments subject to inspection under section 704 that they are requested to submit quality metrics data.

1. Establishments covered by the requests

Except as noted below, FDA intends to request quality metrics data from owners and operators of each establishment that is (1) required to register under with FDA under section 510, and (2) engaged in the manufacture, preparation, propagation, compounding, or processing of the FDF of a covered drug product, or an API used in the manufacture of a covered drug product. For purposes of these requests, a covered drug product would mean a drug product that is:

- subject to an approved application under section 505 of the FD&C Act or under section 351 of the PHS Act.
- marketed pursuant to an OTC monograph.
- a marketed unapproved drug product.

The requests would include (but are not limited to) contract laboratories, contract sterilizers, contract packagers, and other establishments, as appropriate, engaged in the manufacture, preparation, propagation, compounding, or processing of the FDF or API for a covered drug. At this time, these requests do not include excipient or container/closure manufacturers.

Additionally, the requests would not apply to persons and establishments that are not required to register under section 510 of the Act and regulations FDA has issued at 21 CFR 207.10; compounders operating under section 503A or registered as outsourcing facilities under section 503B of the FD&C Act; medical gas manufacturers, positron emission tomography manufacturers, or manufacturers of blood and blood components for transfusion, vaccines, cell therapy products, gene therapy products, allergenic extracts, human cells, tissues, and cellular and tissue based products and non-recombinant versions of plasma derived products. For purposes of this guidance, we will refer to the establishments whose owners or operators are subject to FDA's requests as "covered establishments."

2. Who reports for covered establishments

FDA intends to ask industry to submit one report for each FDF and one report for each API of a covered drug product, which includes quality metrics data from each covered establishment that has the requested data. 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 FDF of a covered drug product or API used in the manufacture of a covered drug product will be under common ownership or control.[17] This establishment should combine the data so that a single report is submitted for each FDF and each API. In this guidance, we refer to the establishments that submit reports to FDA as "reporting establishments."

FDA believes that the quality control unit (QCU)[18] in each reporting establishment for an FDF or API will generally be best positioned to compile reports for submission to FDA, given the unit's responsibilities and authorities for the oversight of drug products as described in 21 CFR 211.22.

FDA recognizes that there may be foreign establishments that are not required to register with the Agency, but have quality metrics data relating to an FDF or API of a covered drug intended for import to the United States. At this time, FDA does not intend to request the submission of quality metrics data directly from such foreign establishments under section 704(a)(4). Instead, covered establishments are encouraged to provide to reporting establishments any of the requested quality metrics data they have or are able to obtain for such foreign establishments, so that the data can be included in the reporting establishments' submissions. The absence of data for such establishments may elevate an establishment's predicted risk in FDA's risk-based inspection scheduling and may increase the likelihood of an inspection. Conversely, reliable

[17] See, e.g., FDASIA section 711; 21 CFR 200.10(b).
[18] For the purpose of this guidance, the term "quality control unit" is synonymous with "quality unit."

data from such facilities may decrease an establishment's predicted risk and reduce the likelihood of an inspection. FDA intends to evaluate these submissions for information about the state of manufacturing and product quality at these foreign establishments and to consider whether to issue broader requests in the future.

As knowledge is gained through this initiative, FDA may consider quality data reporting for additional human drug establishments subject to inspection under section 704 of the FD&C Act.

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. The metrics were identified as being objective, subject to inspection under section 704 of the FD&C Act, and 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, in conjunction with other data accessible to FDA, provide important information about operational reliability and quality culture. Additional, optional metrics, as described below, could provide further detail about quality culture and process capability/performance. In this draft guidance, FDA seeks comment on whether to include the option of submitting these metrics when the guidance is final.

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

- **Lot Acceptance Rate** = 1 – x (x = the number of specification-related rejected lots in a timeframe divided by the number of lots attempted by the same establishment in the same timeframe).

- **Product Quality Complaint Rate** = the number of product quality complaints received for the product divided by the total number of lots of the product released in the same timeframe.

- **Invalidated Out-of-Specification (OOS) Rate** = the number of OOS[19] test results for the finished product invalidated by the establishment divided by the total number of OOS test results divided by the total number of tests performed by the establishment in the same timeframe.

- **Annual Product Review (APR) or Product Quality Review (PQR) on Time Rate** = the number of APRs or PQRs completed within 30 days of annual due date at the establishment divided by the number of products produced at the establishment.

[19] Reference this guidance's Glossary for out-of-specification result.

Additional Request for Comment
Optional Metrics Related to Quality Culture and Process Capability/Performance

FDA is requesting public comment on whether to give establishments the opportunity to submit additional, optional metrics as evidence of manufacturing robustness and a commitment to quality. Data from these optional metrics may merit a reduction in inspection frequency. In addition, FDA intends to consider whether these metrics may provide a basis for FDA to use improved risk-based principles to determine the appropriate reporting category for post-approval manufacturing changes, with emphasis on encouraging lifecycle manufacturing improvement. Comments are requested on the use of optional metrics, the submission of optional metrics, these three specific optional metrics, and any other optional metrics that should be considered.

Quality Culture

FDA acknowledges the importance of quality culture to the overall state of quality of the product, process, and commitment to quality. We also recognize that many companies measure quality culture and encourage this practice. FDA is proposing the following metrics for comment:

- **Senior Management Engagement**: A corporate commitment to quality has been identified in multiple public forums as a strong indicator of a robust PQS. FDA recognizes the difficulties in measuring senior management engagement and support of quality, including manufacturing and facility improvements. Proposed Optional Metric 1 is intended to identify whether senior management with the resources and authority to implement changes are engaged in the assessment of product quality, as well as whether there is shared knowledge of this assessment with the quality and manufacturing organizations. Comments are requested on Proposed Optional Metric 1 and alternative approaches.

Proposed Optional Metric 1:
Was each APR or PQR reviewed and approved by the following: (1) the head of the quality unit, (2) the head of the operations unit; (3) both; or (4) neither?[20]

- **CAPA Effectiveness:** A comprehensive corrective action and preventive action program has been identified as a strong indicator of a robust quality culture. Continual improvement is based on preventing the initial occurrence (preventive action) or recurrence (corrective action) of a detected nonconformity or other undesirable situation. FDA has observed that less robust quality systems often rely on preventing recurrence solely through personnel re-training (i.e., the same training has already been provided to the employee(s)), while more robust quality systems consider re-design and re-development of the process. Comments are requested on proposed Optional Metric 2 and alternative approaches.

[20] See 21 CFR 211.22, 211.25(b), 211.180(e), 211.180(f), 211.192, 211.204, and 211.208.

Proposed Optional Metric 2:
What percentage of your corrective actions involved re-training of personnel (i.e., a root cause of the deviation is lack of adequate training)?[21,22]

Process Capability/Performance

FDA recognizes the importance of statistical process control as a tool in understanding and managing variability in both product and processing for application and non-application products.[23] We recommend that a statistician or person with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures used in measuring and evaluating process stability and process capability. Procedures should describe how trending and calculations are to be performed and should guard against overreaction to individual events as well as against failure to detect unintended process variability.[24] Frequently, however, manufacturing control elements are developed based upon early estimates of process capability at time of product launch or using control strategies considered appropriate at the time of approval. Knowledge gained during scale-up and commercial manufacturing can be useful in further developing the control strategy. It is important that statistical analysis be used to enable and advance product quality, not to inhibit continuous improvement and application of post-launch learning and experience to the assurance of high quality product and consistent processing. FDA requires manufacturers to apply statistical tools in a manner appropriate to assure that the product and process reproducibly meet specifications on an ongoing basis. Specifications must be meaningful in terms of achieving the desired finished product characteristics. This data enables science and risk-based quality risk management by identifying when manufacturing improvement is needed.[25]

Proposed Optional Metric 3:
- A "yes" or "no" value of whether the establishment's management calculated a process capability or performance index for each critical quality attribute (CQA) as part of that product's APR or PQR.[26]
- A "yes" or "no" value of whether the establishment's management has a policy of requiring a corrective action or preventive action (CAPA) at some lower process capability or performance index.
- If "yes" to the above question – what is the process capability or performance index that triggers a CAPA? If "no" to the above question – please do not respond.

[21] See 21 CFR 211.22, 211.100, 211.180(e), and 211.192.
[22] Refer to FDA guidance for industry *Q10 Pharmaceutical Quality System.*
[23] One reference that may be useful is ASTM E-2281, *Standard Practice for Process and Measurement Capability Indices* (2012), ASTM International, West Conshohocken, PA, DOI: 10.1520/E2281-08AR12E01, www.astm.org. This is not the only useful reference on this topic. Many industry standards, books, and guides on these topics are available.
[24] Refer to FDA guidance for industry *Process Validation: General Principles and Practices* (Rev 1).
[25] See 21 CFR 211.110.
[26] See 21 CFR 211.22(c), 211.100, and 211.192.

C. What Quality Data Would Be Reported

Section V.B describes each metric FDA intends to calculate and the associated data that would be used to calculate each metric. FDA encourages reporting establishments to report these data by product and establishment, where applicable, to support FDA's calculation of the metrics described in section V.A.[27] The requests proposed in this draft guidance are for information that we could inspect under section 704 of the FD&C Act, and that we understand is developed and maintained in the course of manufacturing drugs in compliance with current good manufacturing practice. In general, the information needed to respond to FDA's proposed requests is maintained in accordance with 21 CFR 211 subpart J and evaluated under 21 CFR 211.180(e). Additional references are provided to 21 CFR 211 for finished dosage forms. For non-finished dosage form products (e.g., APIs), refer to section 501(a)(2)(B) of the FD&C Act and FDA guidance for industry *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*. FDA would ask for data to be aggregated and reported as described in section V in which is a readily accessible format.

- The number of lots attempted of the product.[28]
- The number of specification-related rejected lots of the product, rejected during or after manufacturing.[29]
- The number of attempted lots pending disposition for more than 30 days.[30]
- The number of OOS results for the product, including stability testing.[31]
- The number of lot release and stability tests conducted for the product.[32]
- The number of OOS results for lot release and stability tests for the product which are invalidated due to lab error.[33]

[27] FDA expects that data associated with contract laboratories will be limited to the number of OOS results, the number of lot release and stability tests conducted, and the number of invalidated OOS.
[28] See 21 CFR 211.165, 211.188.
[29] See 21 CFR 211.192, 165(f).
[30] See 21 CFR 211.188. Under current good manufacturing practice, deviation investigations and final disposition decisions must be completed in a timely manner. Note that the request for lots pending disposition more than 30 days was selected as a measurement tool and not intended to clarify the timely manner in which disposition should be completed. Further, a lot may be subdivided or grouped after the first attempted lot is initiated. Each subsequent subdivision or grouping is considered a separate lot. These data will be used to verify data validity supporting the lot acceptance rate metric.
[31] See 21 CFR 211.160(a). For the purpose of this guidance, this includes: (1) finished product and stability test results *only* and, (2) all finished product and stability test results that initially appear as OOS, even if invalidated by a subsequent laboratory investigation.
[32] See 21 CFR 211.165, 211.194(a), and 610.1. If a lot release or stability test is conducted multiple times for a lot, each test should be counted.

- The number of product quality complaints received for the product.[34]

- The number of lots attempted which are released for distribution or for the next stage of manufacturing the product.[35]

- If the associated APRs or PQRs were completed within 30 days of annual due date for the product.[36]

- The number of APRs or PQRs required for the product.[37]

Reporting of data related to lots of drugs that are imported, intended for import into the United States, or manufactured in the United States or its territories only is preferred. However, FDA recognizes that it may not be possible for some covered establishments and reporting establishments to identify attempted lots, rejected lots, and OOS results that are specific to drugs that are imported, intended for import or manufactured in the United States. In this instance, 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 could be reported 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 and APR/PQR data should be reported related to drugs that are imported, intended for import or manufactured in the United States or its territories.

D. How to Report Quality Data to FDA

FDA intends to request that reporting establishments submit quality metrics data reports for a one-year period that begins after the Agency issues its requests, as specified in the request. Reports would be submitted within 60 days of the end date of the reporting period. For example, if the requests called data for the period October 1, 2016 to September 30, 2017, data reports would be due by December 1, 2017. We intend to request data segregated in the report on a quarterly basis.

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[33] See 21 CFR 211.160(a). While this guidance is requesting data specific to lot release and stability tests, FDA recognizes the importance of other types of testing (e.g., in-process testing, environmental testing, raw material and packaging component testing).

[34] See 21 CFR 211.165,211.198. This quality data is the total number of all product quality complaints, as defined in the Glossary. This does not include multiple counting of the same product quality complaint if the complaint receiver forwards the complaint to individual manufacturers for further investigation.

[35] See 21 CFR 211.150(b).

[36] See 21 CFR 211.22(d); 211.180(e). The data for APRs and PQRs not completed within 30 days was selected as a measurement tool and not intended to clarify the timely manner in which APRs and PQRs should be completed.

[37] See 21 CFR 211.22; 211.180(e).

Appendix A is a quality component list that describes the information that would be submitted to FDA through the FDA Electronic Submissions Gateway (ESG). FDA intends to provide additional technical details in a separate technical specification. Once FDA receives information in response to requests under section 704(a)(4), the Agency intends to issue a confirmation of receipt, in accordance with section 704(a)(4)(B) of the FD&C Act. Any optional metrics would may be submitted using the same method described above. Information included in quality metric data submissions should be submitted in English. FDA believes that segregating reports by quarter and the submission through the ESG on the timetable provided is within reasonable limits and in a reasonable manner.

Data that FDA would request varies by business segment/type and is described in Appendix A.

Additional Request for Comment
Frequency of Quality Metrics Data Reporting

At this time, FDA is considering when it should make additional requests for quality metrics data. Comments are requested on whether to make requests annually or any other possible alternative approaches.

Alternative Approach for Comment
Reducing the Reporting Burden Based on Data Collection Timeframe

FDA is requesting public comment on possible alternative approaches with regard to data collection timeframes to reduce the burden of data collection. For example, FDA is considering whether to use the manufacturer's current timeframe for conducting its APRs or PQRs as a possible alternative timeframe for reporting.

The section immediately above describes reporting for a one-year period which would be the same for all covered establishments, which would be specified when FDA issues its requests. FDA recognizes that APRs and PQRs are often staggered throughout the year. The date on which an APR or PQR is conducted may be based on product launch or, for application products, the application approval date. FDA is requesting public comment on alternative approaches. Data would still be segregated on a quarterly basis within the selected timeframe. Comments are requested on this or any other possible alternative approaches.

Alternative Approach for Comment
Including a Limited Text Field for Data Point/Metrics

FDA is requesting public comment on possible alternative approaches that would enable a company to provide an explanation or plan for continual improvement for reported data points or metrics, while recognizing that FDA may not be able to review each explanation or plan. For example, FDA is considering whether to include a text field for the submission of 100 word "free-text" explanations for each data point or metric.

FDA might review explanatory text submitted as an optional metric to clarify any questions raised in the Agency's analysis of the data. For example, an unexpected decrease in lot acceptance rate may be due to a situation outside the control of the facility (e.g., act of nature like storm or fire). Also, 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 and a temporary increase in total OOS results. However, improved detection that allows for the diversion and rejection of poor quality product will allow for 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).

If this approach is adopted, reporting establishments could elect to include an explanation to identify these types of factors. Reporting establishments could also elect to include a continual improvement plan for the next reporting cycle. Note that FDA will likely be unable to review all submitted comments due to the volume of data that will be reported. However, comments might be helpful during evaluation of the data.

Comments are requested on this or any other possible alternative approaches.

GLOSSARY

Active Ingredient (active pharmaceutical ingredient, API)[38] – any component that 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 of man or other animals. 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.

Annual 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.[39]

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.[40]

Corrective Action and Preventive Action (CAPA)[41]

- **Corrective Action** – an action to eliminate the cause of a detected nonconformity or other undesirable situation.

- **Preventive Action** – an action to eliminate the cause of a potential nonconformity or other undesirable potential situation.

NOTE: Preventive action is taken to prevent occurrence, whereas corrective action is taken to prevent recurrence. (ISO 9000:2005)

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.[42]

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., contract laboratories).[43]

Invalidated OOS – any out-of-specification result that was invalidated. Note: Invalidation of a discrete test result may be done only upon the observation and documentation of a test event that

[38] See 21 CFR 210.3(b)(7).
[39] See 21 CFR 211.180(e).
[40] See 21 CFR 210.3(b)(2).
[41] Refer to FDA guidance for industry *Q10 Pharmaceutical Quality System.*
[42] Refer to FDA guidance for industry *Q8(R2) Pharmaceutical Development.*
[43] See 21 CFR 207.3(a)(7).

can reasonably be determined to have caused the OOS result.[44] For the purpose of this guidance, this includes: (1) finished product and stability test results *only* and, (2) all finished product and stability test results that initially appear as OOS, even if invalidated by a subsequent laboratory investigation.

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]

Lot Attempted – a lot intended for commercial use for which the manufacturer has issued a lot number and charged API (for finished drug manufacturers) or primary starting materials (for API manufacturers).[46]

Lot Release Test – includes all finished product tests, all real time release tests, and all in-process tests that act as a surrogate for finished product lot release.[47,48]

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.[49] For the purpose of this guidance, this includes: (1) finished product and stability test results *only* and, (2) all finished product and stability test results that initially appear as OOS, even if invalidated by a subsequent laboratory investigation.

Process Capability – a statistical estimate of the outcome of a characteristic from a process that has been demonstrated to be in a state of statistical control.[50]

Process Capability Index – an index describing process capability in relation to a specified tolerance.[51]

Process Performance – a statistical measure of the outcome of a characteristic from a process that may not have been demonstrated to be in a state of statistical control.[52]

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[44] See 21 CFR 211.160(a) and FDA guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*.
[45] See 21 CFR 210.3(b)(10).
[46] See 21 CFR 211.101.
[47] See 21 CFR 211.165.
[48] This term does not refer to samples and protocols under 21 CFR 610.2.
[49] See FDA guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*.
[50] See ASTM E-2281, *Standard Practice for Process and Measurement Capability Indices* (2012), ASTM International, West Conshohocken, PA, DOI: 10.1520/E2281-08AR12E01, www.astm.org. This is not the only useful reference on this topic. Many industry standards, books, and guides on these topics are available.
[51] See ASTM E-2281, *Standard Practice for Process and Measurement Capability Indices* (2012), ASTM International, West Conshohocken, PA, DOI: 10.1520/E2281-08AR12E01, www.astm.org. This is not the only useful reference on this topic. Many industry standards, books, and guides on these topics are available.

Process Performance Index – an index describing process performance in relation to specified tolerance.[53]

Product Quality Complaint – a complaint involving any possible, including actual, failure of a drug product to meet any of its specifications designed to ensure that any drug products conform to appropriate standards of identity strength, quality, and purity.[54]

Product Quality Review – a regular quality review, which should normally be conducted and documented annually, of an API with the objective of verifying the consistency of the process and assessment of whether corrective action or any revalidation should be undertaken.[55]

Specification-Related Rejected Lot – a lot that was rejected because it failed to meet at least one specification.

[52] See ASTM E-2281, *Standard Practice for Process and Measurement Capability Indices* (2012), ASTM International, West Conshohocken, PA, DOI: 10.1520/E2281-08AR12E01, www.astm.org. This is not the only useful reference on this topic. Many industry standards, books, and guides on these topics are available.
[53] See ASTM E-2281, *Standard Practice for Process and Measurement Capability Indices* (2012), ASTM International, West Conshohocken, PA, DOI: 10.1520/E2281-08AR12E01, www.astm.org. This is not the only useful reference on this topic. Many industry standards, books, and guides on these topics are available.
[54] See 21 CFR 211.160(b); 211.198.
[55] 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.*

APPENDIX A: INSTRUCTIONS FOR QUALITY METRIC DATA SUBMISSIONS

FDA intends to include these instructions in the requests for quality metrics data described above in section V. At the time such requests are made, FDA intends to provide additional information about mechanisms for submission.

Instructions for Quality Metric Data Submissions – Mandatory Data

1. Provide the drug name referenced in the completed data table.

    a. Drugs that are subject to either approved applications under section 505 of the FD&C Act or under section 351 of the PHS Act and drugs that are covered by a submission to drug master file (DMF) that is intended to support an application – API/drug substance or FDF/drug product name provided in application.

    b. Drugs that are not subject to either approved applications under section 505 of the FD&C Act or under section 351 of the PHS Act – API or FDF drug product name. If the drug product name is included as part of registration, the same name included in registration should be used.

2. Indicate if the drug referenced in the completed data table is prescription or OTC.

    Note: This element is not required to be reported for an API intended for use in the manufacture of a drug product.

3. Indicate the applicable monograph, if any, for the drug referenced in the completed data table.

    Note: This element is not required to be reported for products that are subject to approved, or covered by a submission to a DMF that is intended to support an application, applications under either section 505 of the FD&C Act or under section 351 of the PHS Act.

4. Provide the drug type for the completed data table. This is restricted to two options – API or FDF – only one option can be selected.

5. Provide the applicant name for the completed data table.

    a. Drugs that are subject to either approved applications under section 505 of the FD&C Act or under section 351 of the PHS Act and drugs that are covered by a submission to drug master file (DMF) that is intended to support an application– firm name of the application holder.

    b. Drugs that are not subject to either approved applications under section 505 of the FD&C Act or under section 351 of the PHS Act – N/A.

6. Provide the final labeler name for the completed data table.

    a. Drugs that are subject to either approved applications under section 505 of the FD&C Act or under section 351 of the PHS Act and drugs that are covered by a submission to drug master file (DMF) that is intended to support an application– N/A.

    b. Drugs that are not subject to either approved applications under section 505 of the FD&C Act or under section 351 of the PHS Act – firm name of the labeler listed in the NDC code.

7. Provide the application type for the completed data table.

    a. Drugs that are subject to either approved applications under section 505 of the FD&C Act or under section 351 of the PHS Act and drugs that are covered by a submission to drug master file (DMF) that is intended to support an application– NDA/ANDA/BLA/DMF as applicable.

    b. Drugs that are not subject to either approved applications under section 505 of the FD&C Act or under section 351 of the PHS Act – N/A.

8. Provide the application number for the drug referenced in the data table.

    a. Drugs that are subject to either approved applications under section 505 of the FD&C Act or under section 351 of the PHS Act and drugs that are covered by a submission to drug master file (DMF) that is intended to support an application– approved NDA/ANDA/BLA/DMF number.

    b. Drugs that are not subject to either approved applications under section 505 of the FD&C Act or under section 351 of the PHS Act – N/A.

9. Provide the NDC product code for the drug referenced in the data table.

    a. Drugs that are subject to either approved applications under section 505 of the FD&C Act or under section 351 of the PHS Act and drugs that are covered by a submission to drug master file (DMF) that is intended to support an application– N/A.

    b. Drugs that are not subject to either approved applications under section 505 of the FD&C Act or under section 351 of the PHS Act – final labeled NDC product code.

10. Provide the time period within which the data being reported were collected.

    a. This number should be reported as mm/dd/yyyy – mm/dd/yyyy.

Refer to the companion technical specification for instructions related to data type, format, and range when filling out the remaining information on the data table.

11. Provide the number of "lots attempted," as defined in the glossary, for the drug referenced in (1), segmented by all establishments as described in section V.A and V.D.

Note: If an establishment only performs testing operations, this element is not applicable.

12. Provide the number of "lots rejected," as defined in the glossary, for the drug referenced in (1), segmented by all establishments as described in section V.A and V.D.

Note: If an establishment only performs testing operations, this element is not applicable.

13. Provide the number of lot release and stability "tests conducted," for the drug referenced in (1), segmented by all establishments as described in section V.A and V.D. Lot release test is defined in the glossary.

Note: If finished product or stability testing operations are not applicable to the operations in which the establishment is engaged, this data point is not applicable.

14. Provide the number of "OOS results," as defined in the glossary, for the drug referenced in (1), segmented by all establishments as described in section V.A and V.D.

Note: If finished product or stability testing operations are not applicable to the operations in which the establishment is engaged, this data point is not applicable.

15. Provide the number of "invalidated OOS" results due to laboratory error, as defined in the glossary, for the drug referenced in (1), segmented by all establishments as described in section V.A and V.D.

Note: If finished product or stability testing operations are not applicable to the operations in which the establishment is engaged, this data point is not applicable.

16. Provide the number of "product quality complaints," as defined in the glossary, for the drug referenced in (1), above, segmented by all establishments as described in section V.A and V.D.

Note: This element should not be segmented by establishment and only one value should be reported per quarter. This value should represent all product quality complaints received for the drug referenced in (1), above. It can be attributed to the Reporting Establishment or one of the other establishments listed in the table. If attributed to one of the establishments listed in the table, the Reporting Establishment does not need separate rows.

17. Provide the number of "lots released," as defined in the glossary, for the drug referenced in (1), above, segmented by all establishments as described in section V.A and V.D.

18. Provide a "Yes" or "No" for the question "Was the APR (or PQR) generated within 30 days of the annual due date?" for drug referenced in (1), above, segmented by all establishments as described in section V.A and V.D. Please refer to the glossary for the definition of APR and PQR.

19. Provide the DUNS# for each establishment referenced in the application.

20. Provide the dosage form for the drug that is referenced in (1) – Product Name. The dosage form should be equivalent for all establishments referenced in the application.

    a. **This element is not applicable for establishments that only perform testing operations for the product referenced in the data table.**

21. Provide the FEI # (facility establishment identifier) for each establishment referenced in the application.

    a. **The FEI number should be the same for each quarter (1, 2, 3, and 4) within each establishment.**

22. Select all activity classifications for each establishment referenced in the application. Please restrict the activity chosen for each establishment to the options provided. List the activity name(s) in full (e.g., "Direct Product Manufacturing").

    a. The activity classification should be the same for each quarter (1, 2, 3, and 4) within each establishment.

Worksheet for Data Tables

The tables below are worksheets to support the submission of the data in accordance with the instructions above.

Product Specific Information

Product Name	Rx or OTC	Applicable Monograph	Product Type	Applicant	Final Labeler	Application Type	Application Number	NDC Code	Reporting Time Period

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Establishment	Quarter (1, 2, 3, or 4)	DUNS #	FEI #	# of Lots Attempted	# of Lots Rejected	# of Tests Conducted	# of OOS Results	# of Invalidated OOS Results	# Product Quality Complaints	# of Lots Released	Was the APR Generated Within 30 Days of Annual Due Date?– Yes or No)	How many APR's or PQR's are associated with the product?	Dosage Form	*Activity - Please indicate all that apply - Direct Product Manufacturing, Packager, QC Lab ,Other*
Reporting Establishment Name	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A
Reporting Establishment Name	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A
Reporting Establishment Name	3	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A
Reporting Establishment Name	4	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A
Establishment 1 Name	1								N/A					
Establishment 1 Name	**2**								N/A					
Establishment 1 Name	**3**								N/A					
Establishment 1 Name	4								N/A					
Establishment 2 Name	1								N/A					
Establishment 2 Name	2								N/A					
Establishment 2 Name	3								N/A					
Establishment 2 Name	4								N/A					

Establishment N Name	n							N/A					

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859 **Optional Metrics**

Establishment	Quarter (1, 2, 3 or 4)	Was each APR or PQR reviewed and approved by the following: (1) the head of the quality unit, (2) the head of the operations unit; (3) both; or (4) neither?	What percentage of your corrective actions involved re-training of personnel (i.e., a root cause of the deviation is lack of adequate training)?	V A "yes" or "no" value of whether the establishment's management calculated a process capability or performance index for each critical quality attribute (CQA) as part of that product's APR or PQR.	A "yes" or "no" value of whether the establishment's management has a policy of requiring a corrective action or preventive action (CAPA) at some lower process capability or performance index.	If "yes" to the above question – what is the process capability or performance index that triggers a CAPA? If "no" to the previous two questions – please do not respond.
Establishment 1 Name	1					
Establishment 1 Name	2					
Establishment 1 Name	3					
Establishment 1 Name	4					

Establishment 2 Name	1					
Establishment 2 Name	2					
Establishment 2 Name	3					
Establishment 2 Name	4					
Establishment N Name	n					

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