Draft Guidance for Industry: Request for Quality Metrics

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Stakeholder Technical Webinar
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Speakers

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Objectives

The purpose of this webinar is to:

- Provide an overview of this draft guidance
- Solicit your comments and feedback at the upcoming public meeting and via the docket

Opening Remarks

Janet Woodcock, M.D.

- *Director, CDER*
- *Acting Director, CDER Office of Pharmaceutical Quality*

Overview

- Program goals
- Covered drugs and establishments
- Quality metrics that FDA intends to calculate
- Optional quality metrics
- How FDA intends to use quality metrics
- Sections indicated for specific comments
- Upcoming public meeting

Goals for Quality Metrics

- Promotes responsible practices and quality driven corporate culture
- Identify situations in which there may be a risk for drug supply disruption
- Improve FDA's evaluation of drug manufacturing and control operations
  - To improve the efficiency and effectiveness of establishment inspections
  - Further develop the FDA's risk-based inspection scheduling

Brookings, 2014

Foundation for Quality Metrics

- Industry quality measurement programs are not new
  - At least annual product quality reviews
  - Management reviews
  - Supplier qualification and ongoing monitoring
  - Internal audits

Maturity of QM programs

- Leading vs. lagging indicators
- Develop useful product- and site-specific metrics
- Senior management engagement
- Commitment to quality culture
- Evolution of quality metrics programs over time

Identified Challenges

- Existing metrics are defined differently at different sites
  - Even between establishments operated by the same manufacturer
- Complicated supply chains
- Context matters
  - A single number does not reflect the state of quality

Looking Toward the Future

Goals for FDA's application of Quality Metrics:

- Develop objective measures
  - Quality of a drug product
  - Quality of a site
  - Effectiveness of systems associated with the manufacture of pharmaceutical products

- Conduct continual monitoring, assessment, and reporting on the state of quality across the inventory of drug products and facilities regulated by FDA
  - *Note: Can only be as good as the quality of available data and analytic tools*

Looking Toward the Future

Increasing Operational Flexibility

- Continue to encourage emerging technology
- Exploring ways to reward firms that exceed minimum expectations
- Consider whether metrics may provided a basis to assist in determining the appropriate reporting category for post-approval manufacturing changes

Guidance Format

Five sections:

- Introduction
- Background
- Legal Authority
- How Quality Metrics Will be Used and Effects of Non-Reporting
- Reporting of Quality Data and Calculation of Quality Metrics

Covered Drugs and Establishments

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Who Reports and Who May Contribute to the Report

- Owners or operators of establishments subject to inspection under section 704 of the Act
- In this draft guidance, only certain establishments ("covered establishments") are requested to report data for certain drugs ("covered drugs")

Covered Drugs*

- Finished drug products (FDF)
  - 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
  - Marketed unapproved drug product
- Active pharmaceutical ingredients (API) used in the manufacture of a covered FDF

* For the purposes of this draft guidance

Reports for Covered Drugs*

- At least two reports for each covered drug
  - One report for the finished dosage form (FDF)
  - One report for *each source* of API
    - Multiple reports if multiple sources
- Each report is submitted by a Reporting Establishment
- Reports to be submitted electronically through the Electronic Submission Gateway

* For the purposes of this draft guidance

Covered Establishments*

- Owners and operators of each establishment that is
  - Required to register under section 510 of the Act, and
  - Engaged in the processing, preparation, propagation, compounding, or processing of a covered drug product or API used in the manufacture of a covered drug product
- Includes relevant contract establishments, such as, but not limited to:
  - Contract laboratories
  - Contract sterilizers
  - Contract packagers

* For the purposes of this draft guidance

Reporting Establishments*

- Single establishment that will combine data into a single report
  - One establishment will already possess or have access to all of the quality metrics data needed to submit each report, or
  - All of the covered establishments related to a report will be under common ownership or control
- Quality control unit in each reporting establishment will generally be best positioned to compile reports, given the unit's responsibilities and authorities for the oversight of drug products

* For the purposes of this draft guidance
** Not to scale

Certain Foreign Establishments*

- May be foreign establishments not required to register with FDA, but have quality metrics data relating to a covered drug
- Establishments are encouraged to provide quality metrics data to reporting establishments for inclusion in the report(s)
  - Absence of data may increase the likelihood of inspection
  - Submission of reliable data may decrease the likelihood of inspection

* For the purposes of this draft guidance

Exempted Establishments*

- Persons and establishments not required to register under section 510 of the Act and 21 CFR 207.10
- Compounders operating under section 503A or registered as outsourcing facilities under section 503B of the Act
- Medical gas manufacturers
- Positron emission tomography manufacturers
- 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 the purposes of this draft guidance

Effects of Non-Reporting

- 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
- 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

Quality Metrics that FDA Intends to Calculate

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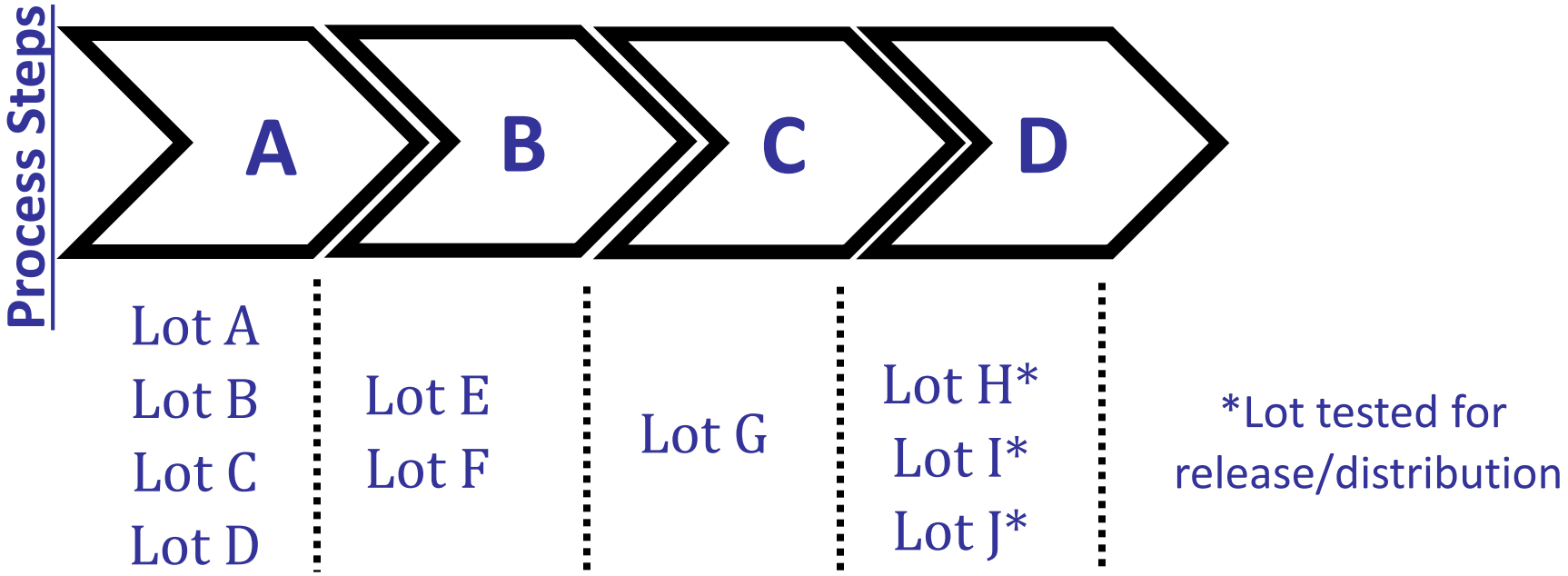
Lot Acceptance Rate

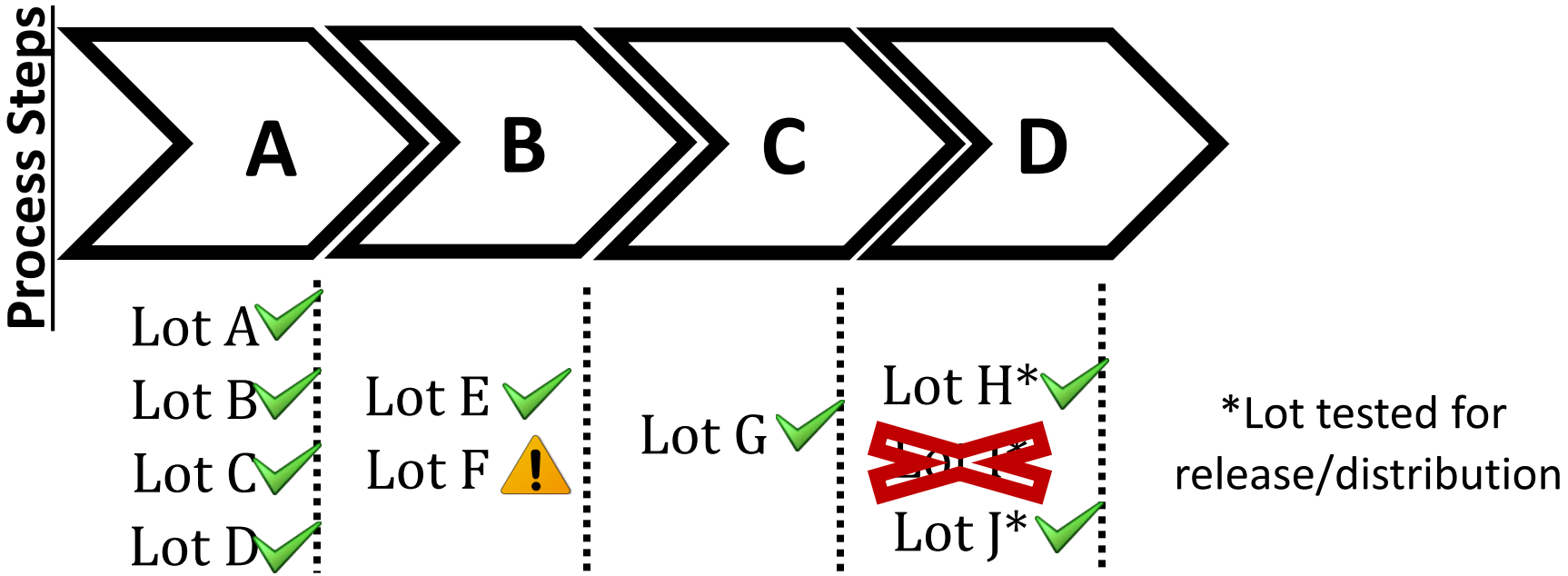
- 1 – x (x = the number of specification-related rejected lots in a timeframe divided by the number of lots attempted by the same establishment in the same timeframe).
  - Specification-Related Rejected Lot
    - A lot that was rejected because it failed to meet at least one specification
  - Lot Attempted
    - 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)

Example: Lots Attempted



Lots Attempted: 10

Example: Lots of Product Released, Number of Attempted Lots Pending Disposition, Number of Specification-Related Rejected Lots



Lots Released for Distribution or for the Next Stage of Manufacturing: 8

Number of Specification-Related Rejected Lots: 1

Number of Attempted Lots Pending Disposition for >30 days: 1

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.
  - 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

Invalidated Out-of-Specification (OOS) Rate

- The number of OOS 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.
  - 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. 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.

Invalidated Out-of-Specification (OOS) Rate

- The number of OOS 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.
  - Invalidated OOS
    - Any out-of-specification result that was invalidated
  - Total lot release and stability tests
    - Lot release tests
      - All finished product tests, all real time release tests, and all in-process tests that act as a surrogate for finished product lot release
    - Stability tests

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.
  - If the associated APRs or PQRs were completed within 30 days
  - The number of APRs or PQRs required for the product

Optional Quality Metrics that May Be Submitted

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Optional Metrics Related to Quality Culture and Process Capability/Performance

- Submission of data/metrics is optional
  - May merit a reduction in inspection frequency

Three questions related to:

1. Senior management engagement
2. CAPA effectiveness
3. Process capability/performance

Senior Management Engagement

- Corporate commitment to quality has been identified in multiple public forums as a strong indicator of a robust PQS

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?

CAPA Effectiveness

- A comprehensive corrective action and preventive action program has been identified as a strong indicator of a robust quality culture.

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)?

Process Capability/Performance

- Importance of statistical process control as a tool in understanding and managing variability in both product and processing for application and non-application products

Optional Metric 3:

- 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.
- 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.

How FDA Intends to Use Quality Metrics

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Uses of Quality Metrics

- Study data to better understand how to interpret metrics
  - Different products at the same establishment?
  - Same product at different establishments?
  - Establishment-specific trend over time?
  - Compare all types of establishments and products or segment by establishment type or product type?

Quality Metrics – Analysis Techniques

Questions

- How to set up a Signal Detection Program to help assess state of manufacturing and product quality?
- To prioritize sites for FDA staff to focus on?
- To prioritize products within a site to focus on?
- Tools to Use?

Sections Indicated for Specific Comment

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Sections Indicated for Comment

- Optional metrics
- Data collection timeframe
- Limited text field
- Frequency of reporting

Upcoming Public Meeting

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Public Meeting

- August 24, 2015
- FDA, White Oak Campus
  - 10903 New Hampshire Ave, Silver Spring, MD 20993
- Live webinar is planned
- Transcript of webinar will be made available after the meeting
- Input requested on the draft guidance and specific questions provided in the Federal Register Notice

Questions for Public Meeting

1. Are there other objective metrics that FDA should request in advance of or in lieu of an inspection that FDA should collect to improve our understanding of products and establishments for purposes of more informed, risk-based inspection scheduling and identification of potential product shortages?
2. Are the definitions of the metrics and associated data requests selected adequate and clear?
3. Are the metrics requested from each business segment/type clear and appropriate?
4. Should the Agency explore collecting metrics from high-risk excipient producers, and if so, which excipients should be considered high-risk and what metrics should apply?

Questions for Public Meeting

5. Should the Agency explore collecting metrics from the medical gas manufacturing industry?
6. Should the Agency add the "Right First Time" metric , and if so, should the definition be a rework/reprocessing rate or a measure of lots manufactured without processing deviations?
7. What data standards/mechanisms would be useful to aid reporting and how should the submissions be structured?
8. Are there reporting hurdles to collecting metrics by reporting establishment/product (segmented by site) versus by site (segmented by product), and how can they be overcome?
9. FDA may consider whether to require the submission of quality metrics on a recurring basis. How frequently should metrics be reported and/or segmented within the reporting period (e.g., annually, semi-annually, or quarterly)?

Summary

- Quality Metrics play an important role in the desired state of pharmaceutical quality and regulation
  - Induce the right behavior and responsibility for industry
    - Identify and reward firms going above and beyond
  - Enable better FDA surveillance of state of manufacturing and product' quality
    - Enhanced site inspection scheduling
    - Potential to improve the efficiency and effectiveness of establishment inspections
  - Help to identify situations in which there may be a risk for drug supply disruption
  - Consider whether metrics may provided a basis to assist in determining the appropriate reporting category for post-approval manufacturing changes

Final Thoughts

- A robust quality metrics program requires continual improvement
  - Ideal metrics are not limited to the metrics in this draft guidance
  - Ideal metrics are specific to the product, site, and supply chain
- The implementation of programs like quality metrics moves us closer to realizing the vision of the Pharmaceutical Quality for the 21st Century Initiative

Additional information

- FDA's Quality Metrics Website:
  - http://www.fda.gov/Drugs/NewsEvents/ucm451529.htm
- Draft Guidance and Notice of Availability:
  - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
  - http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm
- Docket open until XXX, 2015

Thank you