

Draft Guidance for Industry: Submission of Quality Metrics Data

*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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 - *Director, CDER Office of Pharmaceutical Quality (OPQ)*
- *Tara Gooen Bizjak*
 - *Senior Science Policy Advisor, CDER OPQ, Office of Policy for Pharmaceutical Quality*
- *Alex Viehmann*
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Opening Remarks

- *Michael Kopcha, Ph.D., R.Ph.*
 - *Director, CDER Office of Pharmaceutical Quality (OPQ)*



Objectives

The purpose of this webinar is to:

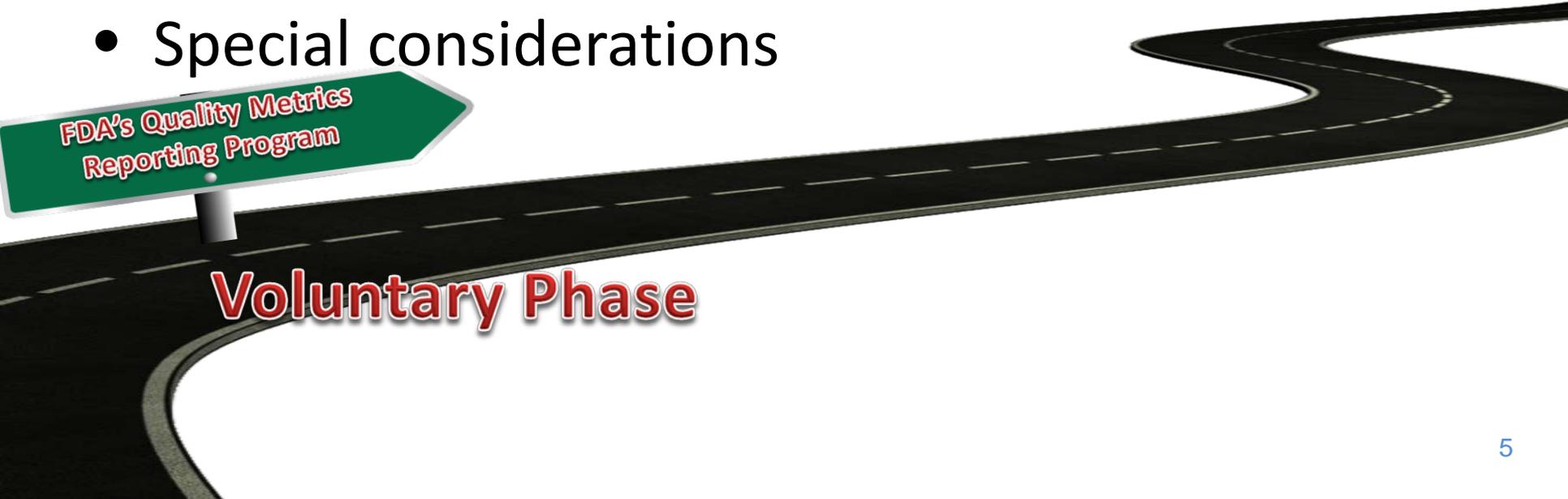
- Provide an overview of this revised draft guidance
- Summarize changes in the revised draft

Overview

- Mature quality metrics programs
- Guidance format
- Changes to the revised draft guidance
- How FDA intends to use quality metrics
- Special considerations



FDA's Quality Metrics
Reporting Program



Voluntary Phase



Mature Quality Metrics Programs

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

Guidance Format

Six sections:

- Introduction
- Background
- Reporting of Quality Data and Calculation of Quality Metrics
- The Use of Quality Metrics and Public Reporting
- Glossary
- Appendix

Product and Site Reporting of Covered Drug Products by Covered Establishments

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Covered Drug Product*

- A covered drug product is:
 - Subject to an approved application under section 505 of the FD&C Act or under section 351 of the PHS Act
 - Marketed pursuant to an OTC monograph
 - Marketed unapproved finished drug product
- This phase of the program is not focused on reporting from certain CDER and CBER regulated manufacturers

* For the purposes of this draft guidance

Covered Establishment

- A covered establishment is:
 - An establishment engaged in the manufacture, preparation, propagation, compounding, or processing of a covered drug product
- Includes relevant contract establishments, such as, but not limited to:
 - Contract laboratories
 - Contract sterilizers
 - Contract packagers



Quality Metrics Data Reports

- Product reports submitted by product reporting establishments
 - The subject of a product report is a covered drug product or an API used in a covered drug product
- OR***
- Site reports submitted by site reporting establishments
 - The subject of a site report is a single covered establishment, individually listing data associated with each covered drug product or API used in a covered drug product

Phased-In Approach and Benefits to Participants

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Legal Basis

- 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
- Quality metrics data described in draft guidance is information of the type that FDA may inspect under section 704 of the Food, Drug, and Cosmetic Act



Submission of Information is Voluntary

- During the voluntary phase of the reporting program, FDA does not intend to require the submission of this information
- FDA does not intend to take enforcement action based on errors in a quality metrics data submission made to this voluntary phase of the reporting program, provided the submission is made in good faith

Disclosure

- FDA does not intend to publicly disclose information submitted to the Agency as part of the voluntary phase of the quality metrics program that is exempt from disclosure under the Freedom of Information Act as confidential commercial information, e.g., information that would reveal nonpublic commercial relationships and production volumes.

Benefits of Participation

- Work with establishments towards early resolution of potential quality problems
- Improved inspection effectiveness
- FDA is considering use of calculated metrics as an element of the post-approval manufacturing change reporting program
- Reduction in inspection frequency
- Inclusion on the Quality Metrics Reporters List



Quality Metrics Reporters List

- Establishments that voluntarily report all or a subset of quality data
 - Product Reporters
 - Site Reporters
- Posted on <http://www.fda.gov/FDAgov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm526869.htm>
- Participation in the program demonstrates:
 - A willingness to proactively engage with the Agency
 - A commitment to increasing transparency between industry and FDA and improving quality monitoring throughout the industry

Quality Metrics that FDA Intends to Calculate, Data Element Definitions, and Examples

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Metrics that FDA intends to Calculate

Robustness of Commercial Manufacturing Process



Lot Acceptance Rate

Robustness of Laboratory Operation



Invalidated Out-of-Specification Rate

Voice of the Patient/Customer



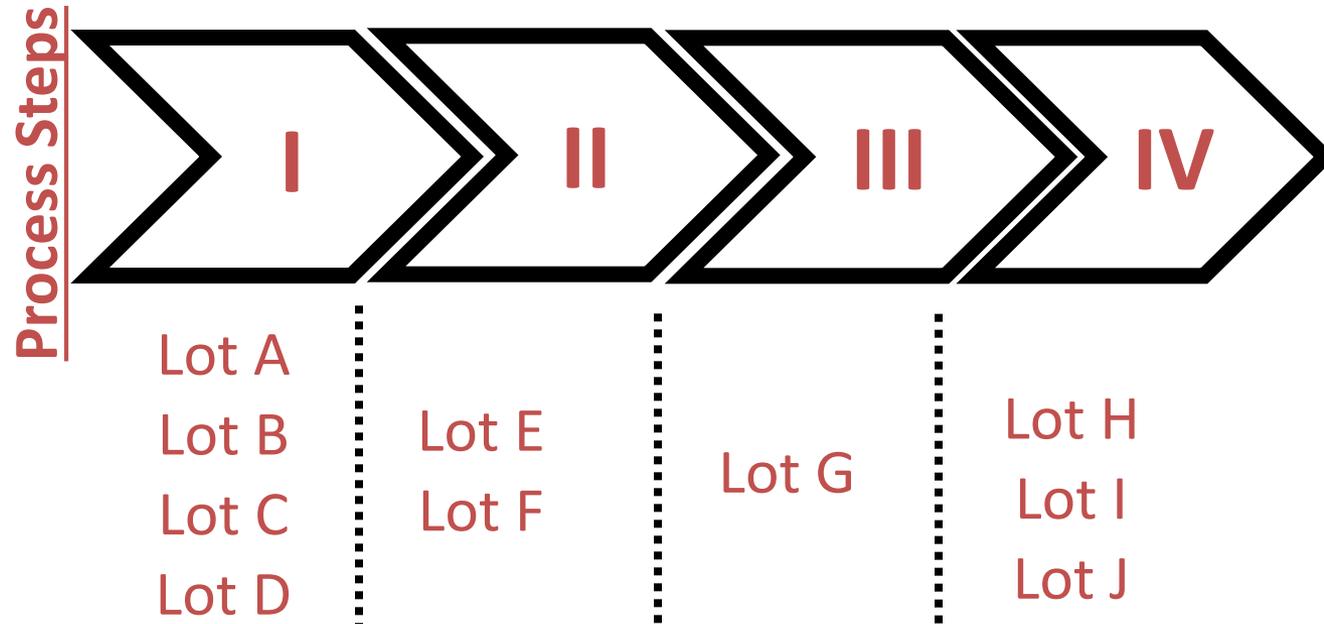
Product Quality Complaint Rate



Lot Acceptance Rate (LAR)

- The number of accepted lots in a timeframe divided by the number of lots started by the same covered establishment in the current reporting timeframe
 - Started Lot
 - A lot intended for commercial use for which the manufacturer has issued a lot number, physically charged API or primary starting materials, and there will be a disposition decision
 - Accepted Lot
 - A started lot which has been released for distribution or for the next stage of processing
 - Rejected Lot
- Separated by saleable lots and In-process and packaging lots intended for distribution*

Example: Lots Started at One Covered Establishment (LAR #1)



Saleable Lots Started: 1 (Lot G)

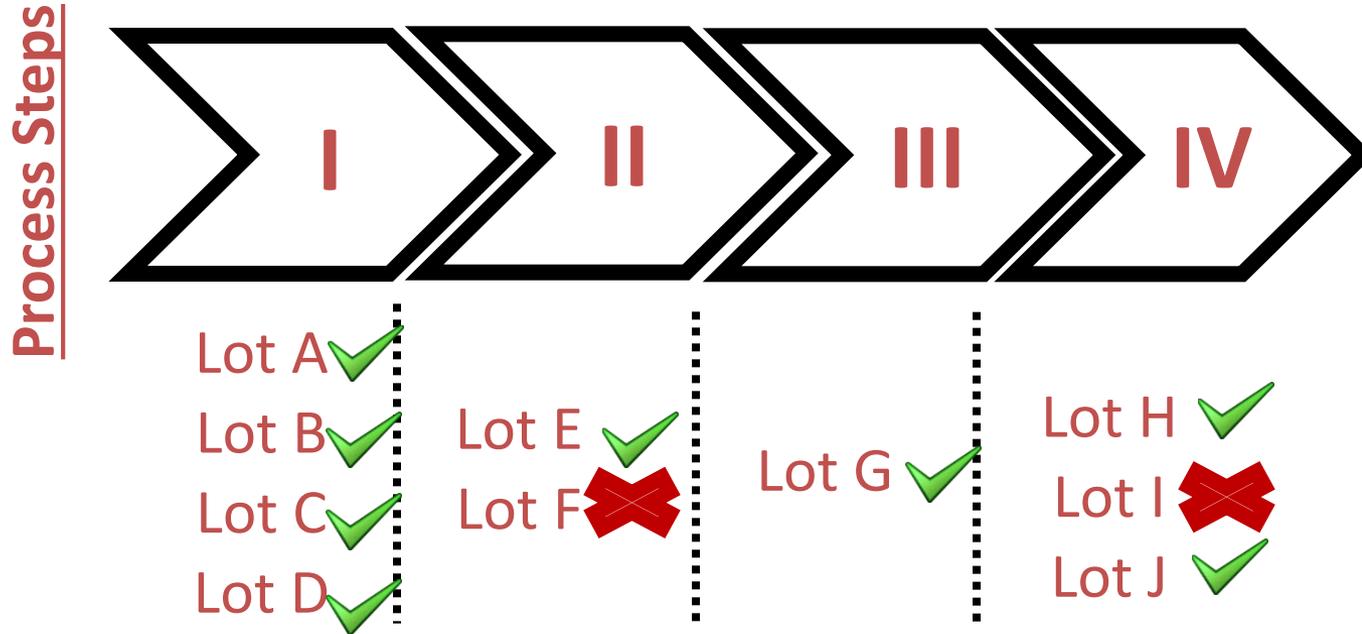
In-process and packaging lots started: 9

I-II: In-process unit operations

III: Unit operation for saleable lot (i.e., finished dosage form)

IV: Packaging unit operation

Example: Lots Accepted and Rejected at One Covered Establishment (LAR #2)



Saleable Lots Accepted: 1 | Rejected: 0

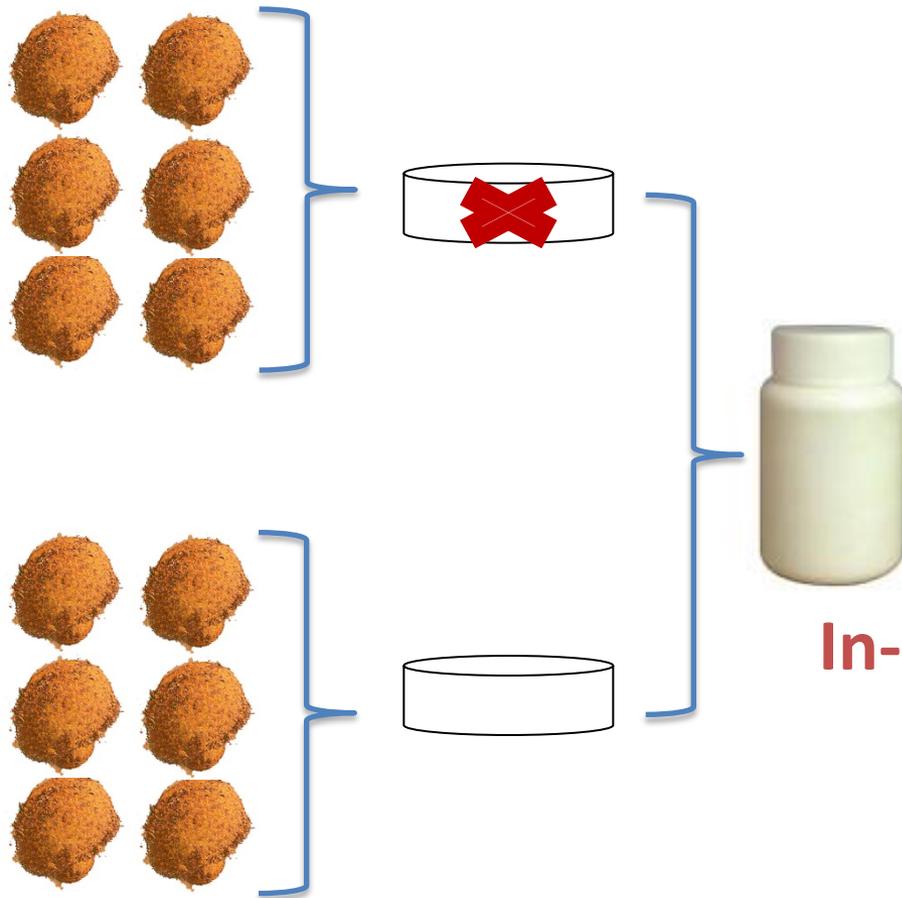
In-process and Packaging Lots Accepted: 7 | Rejected: 2

I-II: In-process unit operations

III: Unit operation for saleable lot (i.e., finished dosage form)

IV: Packaging unit operation

Lot Acceptance Rate: Special Scenarios (LAR #3)

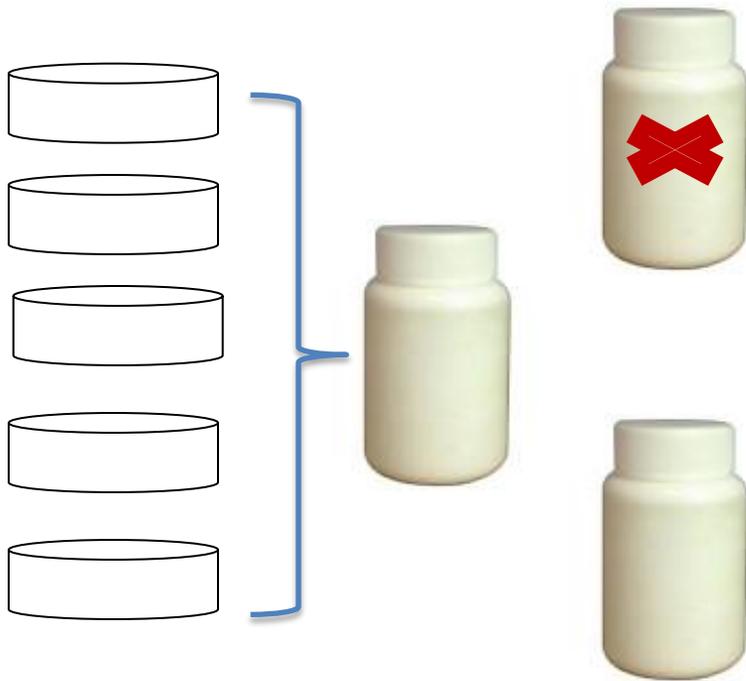


Saleable Lots
Started: 2
Accepted: 1
Rejected: 1

In-process and Packaging Lots
Started: 13
Accepted: 13
Rejected: 0

Blending Lots | Tableting Lots | Bottling Lots

Lot Acceptance Rate: Packaging Site (LAR #4)



Bottling Lots

Saleable Lots
Started: 3
Accepted: 2
Rejected: 1

In-process and Packaging Lots
Started: 0 (N/A)
Accepted: 0 (N/A)
Rejected: 0 (N/A)



Product Quality Complaint Rate (PQCR)

- The number of product quality complaints received for the product divided by the total number of dosage units distributed in the current reporting timeframe.
 - Product Quality Complaint
 - A complaint involving any possible, including actual, failure of a drug to meet any of its specifications designed to ensure that any drug conforms to appropriate standards of identity strength, quality, and purity
 - Dosage Units
 - The total number of individual dosage units, distributed or shipped under the approved application or product family (for non-application products) to customers, including distributors.

Product Quality Complaint Rate (PQCR): Special Scenarios



- If 5 customers report the same type of complaint, we prefer that 5 complaints be counted ^{PQCR #1}
- If 5 different departments from the same customer reports the same complaint, we prefer that 1 complaint is counted ^{PQCR #2}
- If a complaint originates based on a lot sold outside of the United States, we prefer that the complaint is included ^{PQCR #3}

Product Quality Complaint Rate (PQCR): Special Scenarios



- For a site report, if a received complaint is potentially due to the reporter's operations, the complaint *should* be counted ^{PQCR #4}

"Your product is grape flavored and I prefer cherry flavoring."

May Not Be Counted

"Your grape flavored product doesn't taste right."

Count



PQCR #5

Invalidated Out-of-Specification (OOS) Rate (IOOSR)



- Number of OOS test results for lot release and long-term stability tested invalidated by the covered establishment due to an aberration of the measurement process divided by the total number of lot release and long-term stability OOS test results in the current reporting timeframe 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. An investigation must be conducted whenever an OOS result is obtained. For the purpose of the quality metrics program, the following test events should be counted: (1) lot release, including in-process tests that act as a surrogate for a lot release test, and long-term stability test results *only* and, (2) all lot release and long-term stability test results, even if the source of the OOS is later determined to be due to a measurement aberration.

Invalidated Out-of-Specification (OOS) Rate (IOOSR)

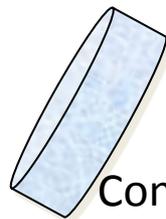


- Number of OOS test results for lot release and long-term stability tested invalidated by the covered establishment due to an aberration of the measurement process divided by the total number of lot release and long-term stability OOS test results in the current reporting timeframe of tests performed by the establishment in the same timeframe.
 - Total lot release and long-term stability OOS results
 - 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
 - Long-term Stability tests
 - Total *invalidated* lot release and long-term stability OOS results
 - Any out-of-specification result that was invalidated as an aberration of the measurement process
 - Total lot release and long-term stability tests

Invalidated Out-of-Specification (OOS) Rate (IOOSR): Special Scenarios



Lot tested at release for:



Assay	PASS
Dissolution	OOS
Impurities	PASS
Content Uniformity	OOS

IOOSR #1

Total Reported OOS: 2
Total Reported Number of Tests: 4

Lot tested on long-term stability for:

	3 mo	6 mo
Assay	PASS	PASS
Appearance	OOS	OOS
Degradation Products	PASS	PASS
Sterility	OOS	OOS



Invalidated via investigation

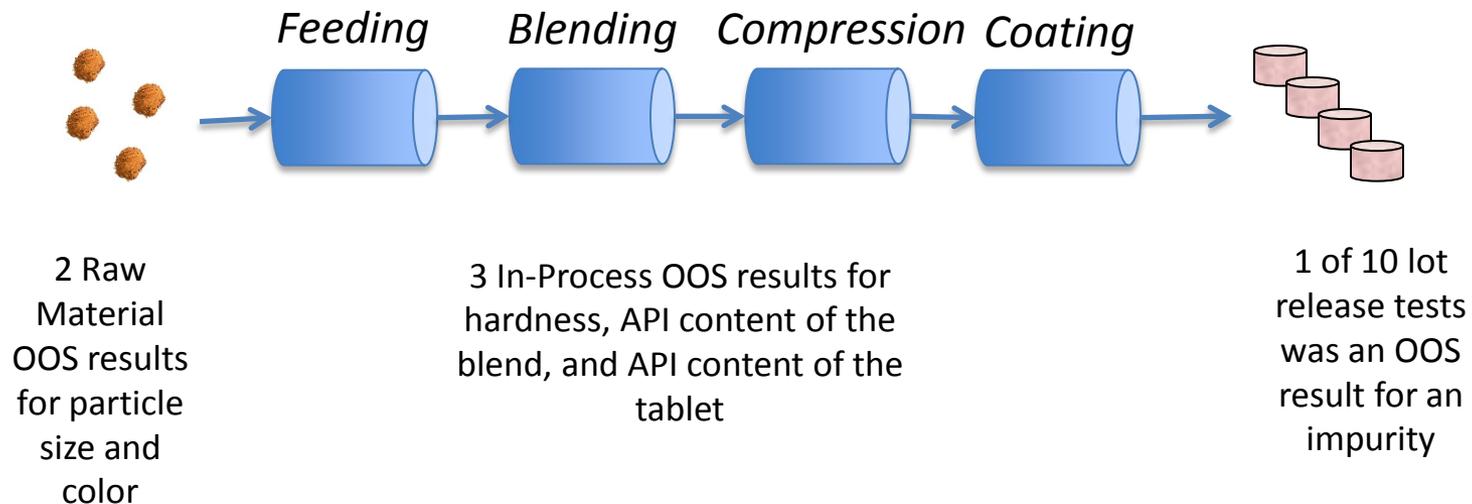
IOOSR #2

Total Reported OOS: 4
Total Reported Invalidated OOS: 2
Total Reported Number of Tests: 8

Invalidated Out-of-Specification (OOS) Rate (IOOSR): Special Scenarios



Continuous Direct Compression Process



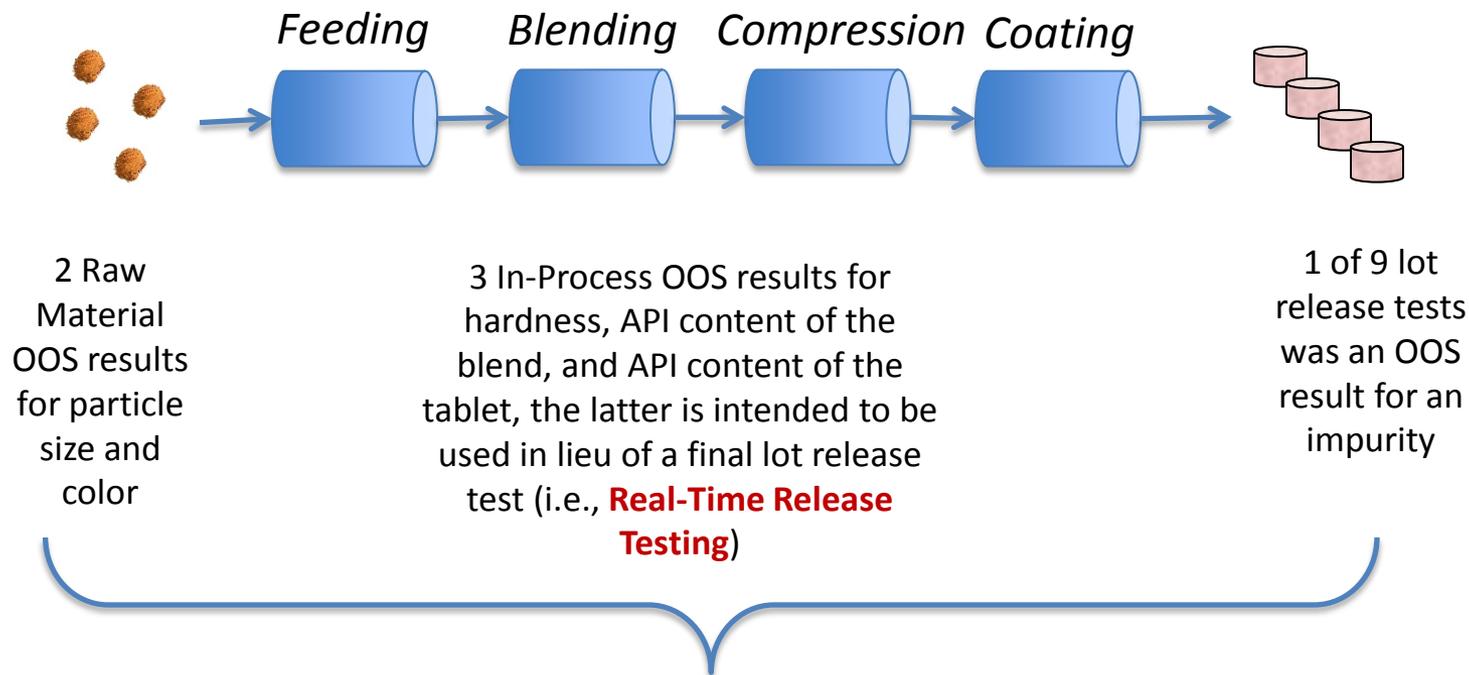
Total OOS Investigations: 6
Total Reported OOS: 1
Total Reported Number of Tests: 10

IOOSR #4

Invalidated Out-of-Specification (OOS) Rate (IOOSR): Special Scenarios



Continuous Direct Compression Process



Total OOS Investigations: 6

Total Reported OOS: 2

Total Reported Number of Tests: 10

IOOSR #5

How FDA Intends to Use Quality Metrics

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Analysis of Quality Metrics Data

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*

*Voluntary reporting may
not constitute a
representative sample of
the industry*

Analytic Objectives

1. Exploratory Studies:

- Examine the relationship between external metrics.
- Examine the relationship between external metrics and internal indicators, as well as look for significant differences.

2. Descriptive Studies:

- Estimate the effect external metrics, as well as internal indicators have on quality responses.

3. Monitoring:

- Monitor the quality of products and sites by utilizing information from exploratory and explanatory studies to detect critical signals (e.g. trends, seasonal effects, cyclic patterns).

Exploratory Studies

Objective: Examine Relationships and identify and explore groups and significant differences

Potential Methods:

1. Univariate – Correlation analysis, Scatterplots, Analysis of Variance (ANOVA)
2. Multivariate – Cluster analysis, Principle Component Analysis

Descriptive Studies

Objective: Estimate the effect external metrics, as well as internal indicators have on quality responses.

Potential Methods:

1. Univariate – Regression analysis (e.g. Ordinal logistic, Binary Logistic, Poisson, etc.)
2. Multivariate – Classification (e.g. Decision tree), Neural Network, Partial Least Squares

Monitoring

Objective: Monitor the quality of products and sites by utilizing information from explanatory and descriptive studies to detect critical signals (e.g. trends, seasonal effects, cyclic patterns).

Potential Methods: Statistical Process Control (Univariate and Multivariate), Time series analysis (e.g. ARIMA), Analysis of Means (ANOM)

Special Considerations

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Addition of Comment Field and Questions

- Optional 300 word field for reporters to provide special context in a report
 - Explanation of submitted data
 - Plans for improvement
- Questions from covered establishments about a specific situation: OPQ-OS-QualityMetrics@fda.hhs.gov

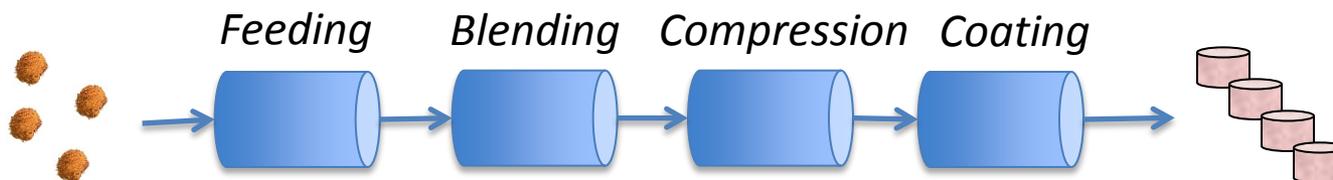
Non-application Products

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

Implementation of New Manufacturing Technology

- FDA supports the adoption of new manufacturing technology
- Industry quality metrics programs can identify which legacy processes could benefit from new manufacturing technology

Continuous Direct Compression Process



Electronic Portal

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Receiving Data via the Electronic Portal

- Defined reporting period (e.g., single calendar year)
- Expect to open the electronic portal to receive reports in early 2018
- Technical Conformance Guide
 - <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/UCM508464.pdf>

Summary

- FDA is issuing this revised draft guidance as part of its overall quality metrics program intended to address common quality issues in the pharmaceutical industry.
- In issuing this revised draft guidance, FDA has reviewed and considered the comments from the public to the first draft guidance.
- This revised draft guidance is intended to be part of an overall program on pharmaceutical quality that will increasingly benefit the industry and the public over time.

More Information/Contacting OPQ

- For more information on this guidance, please see the FDA Quality Metrics website
<http://www.fda.gov/FDAgov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm526869.htm>
- Please provide your comments on the guidance to the docket:
 - www.regulations.gov
- Reach us at: CDER-OPQ-Inquiries@fda.hhs.gov

One Quality Voice