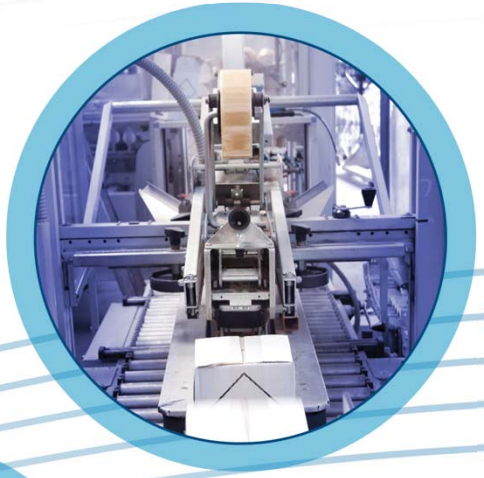
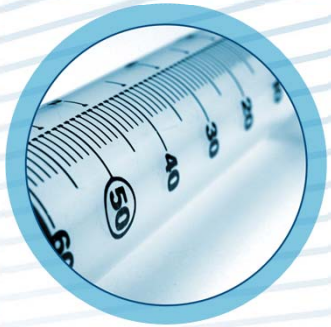
PDA Parenteral Drug Association

Connecting People, Science and Regulation®

Quality Metrics Update Missouri Valley Chapter Meeting April 21, 2014





Linking Drug Shortages and Quality Metrics

- FDAISA (7/12)
  - Title VII, Section 705
    - risk based inspections
- Title VII, Section 706
  - allows for records to be requested in advance or in lieu of inspections
  - Title X, Section 506C-1
    - FDA annual drug shortage report to Congress
- Federal Register 12 Feb 2013
  - Assist in drafting strategic plan on drug shortages

- FDA is exploring use of Quality Metrics
  - for Inspectional Risk Model and
  - possible drug predictor of drug shortages

- PDA's comments to FR sent 13 Mar 13

Understanding Quality Performance

- Vision: A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight
- Use ICH Q10's management reviews:
  - include a broader number metrics
  - drive continuous improvement
  - promoting adoption of new technologies
  - improving process capabilities

- Demonstrated Quality Performance = Privileges
  - Less frequent inspection
  - Preferred handling of Post Approval Changes

Quality Metrics are Important Tools

- Metrics create a dialog to.
  - **Drive continuous improvement**
  - Provide **early detection** of control drifts
  - **Focus resources** on a particular area
  - Ensure a **stable supply of drug product**.

Quality is a Complexity of Standards and Requirements

Quality:

- ICH Q9 – "The degree to which a set of inherent properties of a **product**, **system or process** fulfills requirements"
- ICH Q6 – "The suitability of either a drug substance or drug product for its intended use. This term includes such **attributes as the identify, strength, and purity**."
- Metrics can only capture part of that complexity

No One Set of Metrics Can Act as a Surrogate for Quality

Challenges for Industry

Benefits

- **Greater visibility/transparency** between industry and regulator
- **Drives continuous improvement**
- Audits and inspection schedules can be driven off of trends
- **Prioritize and focus** on the most important issues
- Facilitates **proactive** discussion and action
- Allows for **early identification** of drifts
- Promotes **quality is everyone's job**
- Help **prevent drug shortages**

Risks

- Could drive **unintended consequences**
- Inefficiencies due to excess or complex metrics
- Lead to flawed interpretations if data is not comparable
- Inappropriate (over reaction) responses to metrics **without understanding the context** surrounding the metric.
- Using compliance metrics as Quality surrogate

Metric Types

1. Quantitative (Objective) vs. Qualitative (Subjective)
2. Product Specific vs. Site Quality (System) Metrics
3. Compliance Indicator Metrics vs. Quality Culture Metrics
4. Leading vs. Lagging Metrics
5. External vs. Internal Metrics

Comparing Metrics

- Focus should be on the **trend** and **variability** to drive continuous improvement
  - Comparing metrics between products, sites and companies is **difficult**
  - Adverse trends and variability should trigger further discussions
  - How to deal with changes in Quality Organization and Internal Standards, new product introductions, etc.
- Quality Metrics should not be used as primary evidence of GMP violation that would trigger regulatory action.

Cultural Aspects of Quality Metrics

- Prevent Spinning Data/Falsification
  - For direct comparison, what's in and what's out must be understood
  - Data objectivity and ease of data verification is important
- Preventing Unintended Consequences
- Defining What's to be Accomplished vs. How to Accomplish Metric
- Metric Resource Burden can cut into prevention resources

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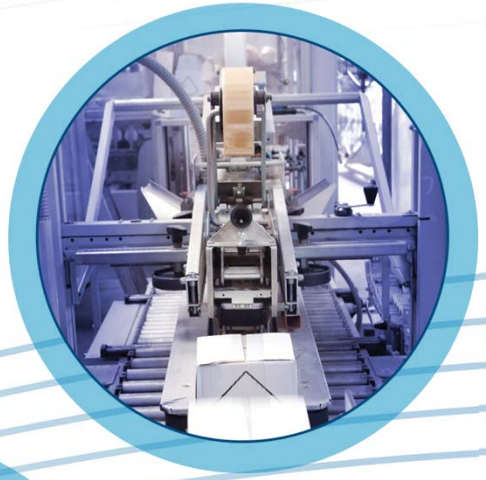
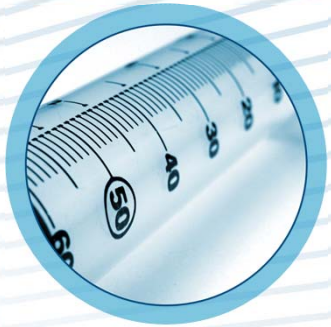
Pharmaceutical Quality Metrics: Definitions and Next Steps





Quality Metric Update & Proposed Definitions

- Summary PDA/FDA joint Conference of 2013
- Commitments
- Quality Metrics Definitions Team
- Proposal for Definitions
- Next Steps

PDA/FDA Conference 2013

- A PDA Task Force together with FDA Held an interactive Workshop with PDA members at the Quality Metrics Conference in December 2013
- The intent was to identify potential quality metrics that industry could provide to FDA in order to prevent and mitigate the risk of drug shortages through application of sections of the FDASIA, specifically:
  - FDA to implement a risk-based inspection regimen
  - FDA to request records in advance of or in lieu of inspections

PDA/FDA Conference 2013

- As a result, the PDA PTC: Pharmaceutical Quality Metrics document was published to capture the consolidated opinion and recommendations on quality metrics from more than 300 attendees representing views from approximately 150 companies and scientists representing global perspectives in pharmaceutical, biological, and device manufacturing and quality

Commitments from Quality Metrics Conference

- Update the PDA PTC with proposed metrics definitions
- Conduct a Survey/Pilot for Metric Collection
- Hold a follow up conference in 2014

OUR INTENT TODAY: Start a dialogue with membership on proposed metrics definitions

Formed a Quality Metrics Definition Team

- Anil Sawant, J&J
- Anders Vinther, Genentech
- Denyse Baker, PDA
- Edwin Martinez-Rivera, Sanofi
- Gabriele Gori, Novartis
- John Farris, Amgen
- Joyce Bloomfield, Merck & Co Inc.
- Pritesh Patel, Allergan Inc.
- Susan Schniepp, Allergy Labs

Quality Metric Definition Proposal

- The team focused on the seven (7) Quality Metrics recommended for FDA collection in the PTC document
- For each metric, the team proposes:
  - A definition to consider
  - How to calculate the metric
  - How to report the data
  - Unintended consequences to consider

Metrics Proposed by PDA

- Complaints by Product
- Batch Reject Rate by Product
- Batch Reject Rate by Site
- OOS Rate by Product
- OOS Rate by Site
- Recalls by Product
- Recalls by Site

Principles Used to Report By Product and By Site

- By Product
  - *Product = all items with same formula, irrespective of packaging configuration*
  - *Each DS batch, is also a "product batch" for counting purposes*
  - *Does not include raw materials, incoming components, or 3rd party purchased items.*
- By Site
  - *Compilation of the all 'by product' values at a single manufacturing site.*
  - *Combines metrics from all DP and DS batches manufactured at the site.*
  - *CMOs report metrics from their sites. (CMO does not report recalls if the specific issue or root cause is caused by the MAH.)*
- Reporting
  - *Collect monthly and report annually; product metrics with APR or Annual Report cycle*
  - *Possibly include last x months of product or site data with a post approval change submission*

Product Quality Complaint Rate

- Calculation
  - *Complaints / Million Units Distributed*
  - *Numerator = All Customer Complaints received at manufacturer*
  - *Denominator = Individual Units Distributed containing drug product/one million.*
  - *Timeframe = monthly*
- Reporting
  - *By Product only*
  - *Collect 24 data points and report once per year (12 numerators, 12 denominators)*

Product Quality Complaint Rate (cont.)

- Potential Unintended Consequences
  - *Manufacturers might re-define Complaints vs. Inquiries*
  - *Separation of elegance issue vs. complaint could differ among companies and markets*

Batch Reject Rate

- Calculation:
  - *Batch Rejection Rate as a percent = number of rejected batches x 100/total number of commercial batches dispositioned during one reporting period.*
- Definitions:
  - *'Rejected' = a disposition decision indicating that the batch did not meet the requirements of the marketing authorization and any other regulations relevant to the production, control and release of the medical device or medicinal product. Includes abandoned batches.*
  - *'Dispositioned' = the final product output (released, held, abandoned, or rejected) from the site that is initially planned for commercial use, regardless of manufacturing stage (e.g., intermediate, bulk, or finished drug product)*

Batch Reject Rate (cont.)

- All batches started should be dispositioned as defined above. Start of batch manufacture must be defined by each firm. Generally, same as for hold time calculations.
- Includes validation batches intended for commercial use (pre-designated).
- Site metric includes only those batches manufactured and/or packaged at the reporting site. A DS batch rejected counts against the DS site.

- Potential Unintended Consequences
  - May make smaller lots, hence increasing the denominator.
  - May not totally reject the batch; could divert it for validation or engineering batch, not for sale,
  - May delay rejection/disposition into a more favorable period
  - May not designate batch for commercial use until after complete testing is done.

Confirmed OOS Rate Definition

- *Confirmed OOS = cases where the investigation indicates an OOS result is caused by a factor affecting the batch quality and the result should be used in evaluating the quality of the batch or lot.*
- *A confirmed OOS result indicates that the batch does not meet established standards or specifications and should result in the batch's rejection, in accordance with 211.165(f), and proper disposition. (from FDA's October 2006 OOS Guidance)*
- *Percentage of confirmed OOS per all Drug Substance (DS) or Drug Product (DP) batches tested in a pre-determined timeframe*
- *Stability OOS are reported separately from Release OOS.*

Confirmed OOS Rate Calculation

- *Number of Confirmed OOS x 100/total number of DS or DP batches manufactured that are tested in the reporting timeframe.*
- *Counted when the OOS investigation has been completed and a final decision is made regarding the disposition of the batch and all the specification test results are available and confirmed.*

Confirmed OOS Rate Calculation (cont.)

- Included
  - *Batches of U.S. licensed DS or DP which are not for the US market, but which have the same specifications.*
  - *Confirmed OOS at external labs are reported against the site of manufacturing.*
- Not Included
  - Process Deviations (e.g. EM excursions, Utilities deviations, medial fill failures)
  - OOS on raw materials or incoming components, or 3rd party purchased items.

Confirmed OOS Rate - Reporting

- Measured monthly, Reported annually, by product and by site
- Firm should comment on or explain any trends observed
- Site/Firm should include their definition for batch or lot which should be consistent throughout the site, throughout the reporting period, and between reporting periods.

Scenario: OOS found on stability DS manufactured by a CMO and used by an innovator in DP. Who reports this?

Confirmed OOS Rate - Unintended Consequences

- Could report tests results later to move their impact to a different reporting time period.
- In the case where a client requires a different specification from the release specs (i.e., higher purity API), a site could choose to only report OOS to the less stringent specification.
- Could include tests which are not part of the registered specifications, to “dilute” the OOS rate
- Might exclude tests for batches which are diverted to engineering or technical purposes after identification of the OOS
- Could include incorrect «non confirmed» OOS test results
- Might use inconsistent definition of a batch/sub-batch when apply CFR 210 or CFR 820
- Might use a different interpretation of which tests are in scope or not in scope with the purpose of improving the rate (e.g. external labs, third party provided materials and API’s, EM)

Recalls

Definition

- *Total number of product batches recalled vs. versus total number of batches manufactured and distributed*
- Metric by Site
  - *Provides data specific to a site relevant to potential shortage*
  - *Reported by manufacturing site including CMO.*
  - *CMO does not report if the specific issue or root cause is caused by the MAH (Market Authorization Holder); MAH would report as part of product metric*
- Metric by Product
  - *Provides data specific to a product relevant to potential shortage*
  - *MAH (Market Authorization Holder) reports to FDA including CMO data on same product; CMO doesn't report*

Recalls (cont.)

Calculation

- Ratio of total number of batches recalled : the total number of batches distributed

Reporting

- By product and by site
- Provide both values to FDA.
- Timeframe: Collected monthly; report annually

Potential Unintended Consequences

- Recalls may not be directly associated with a GMP related issue may be included (eg. post market clinical studies)
- Recalls may be market dependent – may not have to recall for given issue in another market
- Reason for recall may not be product specific

Next Steps

- Collect membership feedback on proposed definitions and update the PDA PTC
- Conduct a Survey/Pilot for Metric Collection
- Hold a follow up conference in 2014