Quality Metrics Journey
2016 CBI Product Complaints Congress

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• ISPE Quality Metrics Core Team
• PCPC Quality Assurance Committee
Journey to ...
Journey Mileposts

1. FDA Quality Metrics Overview
2. ISPE Quality Metrics Journey
3. Metrics that Matter
4. Complaints ... a Competitive Advantage
FDA Quality Metrics
Overview

Drug Products
Potential Benefits

- Reduced Inspections
- Reduced Drug Shortages
- Reduced Regulatory Oversight for post-approval changes

✓ Accelerated Continual Improvement
FDA Draft Guidance

• Covered & Reporting Establishments

• Metrics
  • 4 Required Metrics
  • 3 Optional Metrics

• Data Reporting
  • Product differentiated by site
Reporting Establishment

• One report for each API or for each Finished Dosage Form
• Challenges with complex supply chains

Establishment 1 (bulk manufacturing) → data → Establishment 2 (packaging) → data → Establishment 3 (testing) → data

Reporting Establishment submits one report to FDA
Required Metrics Data to Report

- Number of lots attempted
- Number of specification-related rejected lots
- Number of attempt lots pending disposition >30 days
- Number of OOS results invalidated due to lab error
- Number of lot release and stability tests
- Number of OOS results
- Number of product quality complaints for the product
- Number of lots attempted which are released for distribution or for the next stage of manufacturing
- Whether the associated APRs or PQRs were completed within 30 days of annual due date for the product
- The number of APRs or PQRs required for the product
Quality Metrics Calculated by FDA

- **Required Metrics**
  - Lot Acceptance rate
  - Product Quality Complaint rate
  - Invalidated Out-of-Specification rate
  - Annual Product Review On Time rate

- **Optional Metrics**
  - Senior management engagement in APRs
  - CAPA effectiveness (% for re-training)
  - Process capability/performance questions
Quality Metrics Defined

• Lot Acceptance Rate

\[
\frac{1}{\text{Lots Attempted}} - \frac{\text{Lots Rejected for Failing a Specification}}{\text{Lots Attempted}}
\]

• Product Quality Complaint Rate

\[
\frac{\text{Number of Product Quality Complaints}}{\text{Lots Released}}
\]
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
Quality Metrics Defined

• Invalidated OOS Rate

\[ \frac{\text{# of Invalidated OOS FP Test Results}}{\text{# of OOS FP Results}} \]

\[ \frac{\text{# of OOS FP Results}}{\text{# of FP Tests}} \]

• Annual Product Report on Time Rate

\[ \frac{\text{# of APQRs Completed within 30 days of Due Date}}{\text{# of APQRs Due}} \]
Timing

• Comment period on Draft Guidance closed Nov ‘15

• When will the Final Guidance will be issued?
PCPC, CHPA & ISPE Comments

• Start small – 3 metrics (drop APR On-time Rate)
• Do not include API reporting or Optional Metrics to start
• Voluntary during learning period
• Align reporting with common industry practice (primarily by site)
• Allow grouping of formula (similar to APRs) for reporting
• Clarify definitions
• CMOs report directly
• Importance of Context
How does FDA intend to use quality metrics?

Develop objective measures

Quality of a drug product

Quality of a site

Effectiveness of systems associated with the manufacture of pharmaceutical products
How does FDA intend to use quality metrics?

Appropriate comparators may vary

- Compare same metric, same product, same establishment over time?
- Compare same metric, different products, same establishment?
- Compare same metric, establishments performing same unit operation?
- Compare same metric, products in the same class (e.g., large molecule injectables)?
- Other?
How does FDA intend to use quality metrics?

- Identify risk-based factors that could impact inspection frequency
- Improve detection of manufacturing conditions that may lead to a shortage
- Monitor site and product level performance over time
- Use in conjunction with other sources of information about product and site quality
  - Inspection results
  - Recalls
  - Field Alert Reports/Biological Product Deviation Reports
Summary

• Quality Metrics play an important role in the desired state of pharmaceutical quality and regulation
  • 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 provide a basis to assist in determining the appropriate reporting category for post-approval manufacturing changes
ISPE Quality Metrics Journey
Quality Metrics Timeline

- **July 2012**: FDASIA signed into law
- **2012**: Industry Whitepapers
- **2013**: Launch Wave 1 Pilot
- **2014**: Brookings Institute
- **2015**: Launch Wave 2 Pilot
- **2016**: FDA FRN/Draft Guidance
- **Beyond ...**:

We are here
Wave 2 Pilot – Objectives

- **Expand** data set across segments and geographies to further *learning* from Wave 1 and evaluate *trending* patterns
- Test proposed FDA metrics
- Evaluate effort to report at a product level
- Continue to develop measures and tools related to Q Culture and Process Capability
- Continue data-driven dialogue with regulators
ISPE Quality Metrics Wave 2 Pilot Timeline

Wave 2 Pilot enrollment  Data collection and submission  Industry analysis  Individual reports

Launch

Jun 2015

Wave 2 pilot Report

May / Jun 2016

83 Sites, 28 Companies
Enhanced geographic, technology and product type representation
## Wave 2 Metrics

### External Quality Outcomes
- Total complaints rate
  - Per million packs, incl. LOE
  - Per million packs, excl. LOE
  - Per ’000 attempted lots released, incl. LOE
  - Per ’000 attempted lots released, excl. LOE
- Critical complaints rate
  - Per million packs
  - Per ’000 attempted lots released
- Total recall events per year

### Internal Quality Outcomes
- Lot acceptance (%)
  - Per finally dispositioned lots
  - Per attempted lots
- Invalidated OOS rate
  - Per ’000 lots tested
  - Per ’000 tests performed
  - Per total OOS per tests performed
- Right first time (%) per released lots attempted
- Deviations rate
  - Per ’000 finally dispositioned lots
  - Per ’000 attempted lots
- Recurring deviations rate (%)
- Lots pending disposition more than 30 days (%) per lots attempted

### Culture Indicators
- Culture survey scores (% top boxes)
  - Total score
  - Leadership score
  - Integrity score
  - Mindset score
  - Governance score
  - Capabilities score
- CAPAs with preventive actions (%)
- Planned maintenance rate (%)
- Employee turnover rate (%)
- Human error deviations (%)
- Deviations with no assigned root cause (%)
- CAPA requiring retraining (%)

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**SOURCE:** ISPE Quality Metrics Initiative
The fine print . . . in large font

- Correlation is not causation
- “Hidden” influence of variables and factors not in pilot
- Sample is not the full population
- Consistent rules for outliers vs. subjective judgement
- Statistical significance of the relationships
- Strength of the relationship meets realistic expectations for these metrics
- Meeting the common sense test
- Findings are directional, more work needed

SOURCE: ISPE Quality Metrics Initiative
Wave 2 Correlations Overview

**SOURCE:** ISPE Quality Metrics Initiative

- **External Quality Outcomes:**
  - Total Complaints (per pack)
  - Total Complaints (per Released Lots)

- **Internal Quality Outcomes**

- **Culture Indicators:**
  - Planned Maintenance Rate
  - CAPA with Preventative Actions

**Correlations with p-value <0.05**

**FRN metrics**
Planned Maintenance Rate & Product Q Complaints Rate

Planned maintenance rate to total complaints (n=15 solids sites)

<table>
<thead>
<tr>
<th>Total complaints rate (including LOE) per million pack</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned maintenance rate, %</td>
</tr>
</tbody>
</table>

Note: Major outliers excluded – more than 2 interquartile ranges away from sample median – 2 sites excl. on total complaints both with very high LOE rates

$R^2$ measures to what extent metric Y (dependent variable) is explained by the variability of metric X (independent variable)

P- value is probability that correlation between X and Y is zero, value below 0.05 indicates statistically significant results.

SOURCE: ISPE Quality Metrics Initiative

- Planned maintenance rate explains ~45% of the variability in total complaints per million packs
- This relationship may be related to the common factors that influence both planned maintenance rate and total complaints – such as focus on prevention, operational excellence, quality improvement mindset
FDA Guidance Metrics Definitions

Product Quality Complaint Rate – proposed normalization by packs released

– When normalized by released lots attempted has no connection to other quality metrics

– When normalized by packs there is correlation to cultural metrics

SOURCE: ISPE Quality Metrics Initiative
ISPE Quality Metrics Initiative

Quality Metrics Pilot Program
Wave 2

June 2016

Now Available
Metrics that Matter
Global Consumer Contact Facts

- 60 Billion consumer units shipped
- 4 million consumer contacts
- 2 million consumer complaints

50% Consumer Complaints
50% Testimonials, Inquiries & Availability Comments
Consumer Comment Statistics

Less than 5% have or likely have a root cause in manufacturing or design
OTC Complaint Reality

• Wide variability in the Quality of information due to the reporting process (consumer vs. medical professional)

• Only 50% of consumers have product at time of reporting -> difficulties in identifying the specific product and lot code

• Financially motivated fraud artificially inflates the numbers of complaints

• New product launch and change result in an increase in complaints
Consumer Comment Journey
ADVERSE EVENT
100% of AE CASES ARE REVIEWED BY GSSA

NON-SERIOUS AE

SERIOUS AE

VALID LOT CODE

INVALID LOT CODE

CRITICAL PQC’s

NON-CRITICAL PQC’s

PLANT AND/OR R&D INVESTIGATION

MONTHLY SIGNAL DETECTION & ANALYSIS

INVESTIGATION CONTINUES VIA SIGNAL DETECTION

SYSTEM CHECK FOR CAPA QUALITY ALERTS IN TARGETED BUSINESSES.

INQUIRIES, TESTIMONIALS & AVAILABILITY REQUESTS
Data Mining Consumer Complaints

• Multi-Item Gamma Poisson Shrinker analysis leads to greater regulatory compliance & improved design input

• Fully automated interactive dashboards and document tracking systems

• More time for in-depth analysis and investigation
Signal Detection

Antiperspirant/Deodorant Issue

• Affects cream formulas for all brands

• Consumers describe:
  • Hard particles/contamination
  • Gritty/sandy/lumpy/dried out texture
  • Crumbling sticks or residue
  • Some have associated Adverse Events
Lot-to-Lot Example

- Bounty Paper Towels: Dissatisfied with Performance
- Root cause: Experimental Run was Shipped
  - Too much surfactant → Towels felt sticky
Detecting Potential Fraud

- Repeat complainers edit their addresses to appear as different households. They register multiple complaints asking for coupons and gift cards.
- Cluster analysis groups similar addresses into unique households & identifies repeater networks

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**Cluster Analysis on Addresses**

- 123 fake st.
- 123 fake st
- 123 fake st
- 123 fake st
- 123 fake st
- 123 fake st
- 123 fake st

Repeaters

Repeater Networks

Each node represents a physical address. The connecting lines mean the two addresses have the same email on file. Orange dots are known repeaters.
Detecting Potential Fraud

Consumers find complaints online, change a few words, and submit complaints – text mining allows detection of these “Copy Cats”
Complaints ... A Competitive Advantage
What If?

You went to work on Monday and found out that you now work for Marketing?
HUG YOUR HATERS
How to Embrace Complaints and Keep Your Customers
JAY BAER
New York Times bestselling author of YouTility

HATERS ARE NOT YOUR PROBLEM...
IGNORING THEM IS

@JayBaer
92% Use social media
75% Own a smartphone

Phone: 91%
Email: 89%
Expect Reply: 42%
Boost in Advocacy: 20%
Decline in Advocacy: -43%
Onstage Complaints by Venue: 29%

95% Use social media
79% Own a smartphone

Social Media: 53%
Review Sites: 16%
Boards/Forums: 25%
Onstage Complaints by Venue: 55%

Edison Research and Jay Blas: 2015
Strategies

- Prevention
  - Proactivity
  - Solicit Complaints
  - Satisfy Complainants
  - Integrated VOC
Deliver Psychic Pizza

You got 30 minutes and you got Domino's Pizza headed your way. Our delivery experts have specifically engineered the Pizza Tracker to keep you up to date on the status of your order from the moment it's prepared to the second it leaves our store. You got tracking where tracking has never gone before.

**YOU GOT ORDER ASSEMBLY - YOUR ORDER WAS BOXED FOR DELIVERY AT 12:37 PM**

**YOUR LOCAL STORE:**
Contact your Domino's with any questions:
2282 South Main Street
Ann Arbor, MI 48103
734-332-1111

**YOUR ORDER DETAILS:**
1. Small (10") Hand Tossed Pizza
   - Extra Cheese, Sauce, Pepperoni, Italian Sausage.
2. Chicken Kickers
3. 2-Liter Coke

**RATE YOUR DOMINO's**
When your pizza arrives tell us how it was.
(Rate our service from 1-5)

*Store average: ★★★★  LEAVE US A MESSAGE*
What if the biggest risk to your business were those people who don’t complain?
Satisfy Complainants

#1 Complaint for Dental Floss: the floss shreds/breaks
Different Types of Floss

**Multi-filament**
strands of nylon floss

**Mono-filament**
one strand of rubber, plastic, PTFE*

*PTFE = Polytetrafluoroethylene
Changing How We Respond

• **Old Response:**
  
  • We are sorry to hear about your experiences. P&G is dedicated to deliver consumer satisfaction. Please accept this coupon for a replacement product.

• **New Response:**
  
  • We are sorry to hear about your experiences. P&G is dedicated to deliver consumer satisfaction. *We have a different floss product that will address your needs.* Please accept this coupon for a new product to try.
Integrated VOC
Where is Your Journey Headed ...

Compliance or Value?