FDA/CDER’s Evolving Approach to Quality and the Use of Metrics

Russell Wesdyk
CDER/OSP
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RATIONALE FOR PROPOSED OFFICE OF PHARMACEUTICAL QUALITY
Vision for 21st Century Manufacturing

“A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.”

Are we there yet?
FARs – State of Quality?

FAR Receipts By Year

2005 2006 2007 2008 2009 2010 2011
Recalls – State of Quality?

Number of Product Recalls: 2002-2012
for Prescription and OTC Products

Source: FDA CDER Office of Compliance, Date Extracted: June 28, 2012
Drug Shortage – State of Quality?

U.S. Drug Shortages

- All Dosage Forms Shortages
- Sterile Injectable Shortages

Yearly Breakdown:
- 2005: 61
- 2006: 56
- 2007: 41
- 2008: 44
- 2009: 35
- 2010: 46
- 2011: 178

Total Shortages: 251

Reasons for Shortage 2011:
- Component Problems: 47%
- Delays/Capacity Issues: 19%
- Discontinuation: 12%
- Increased Demand: 10%
- Loss of Manufacturing Site: 4%
- Other/Unknown: 2%
- Quality Issue: 0%
- Raw Materials (API): 4%
NDA Supplements

Time Series Plot of FY 2000-2008 supplements per approved application

Supplements per approved application

Year post approval

Variable

- FY 2000 % of approved
- FY 2001 % of approved
- FY 2002 % of approved
- FY 2003 % of approved
- FY 2004 % of approved
- FY 2005 % of approved
- FY 2006 % of approved
- FY 2007 % of approved
- FY 2008 % of approved
ANDA Supplements

Time Series Plot of FY 2000-2012 suppl recvd per approved ANDA

Variable
- FY 2000 norm
- FY 2001 norm
- FY 2002 norm
- FY 2003 norm
- FY 2004 norm
- FY 2005 norm
- FY 2006 norm
- FY 2007 norm
- FY 2008 norm
- FY 2009 norm
- FY 2010 norm
- FY 2011 norm
- FY 2012 norm

Supplements recvd per approved ANDA

Year post approval

0 1 2 3 4 5 6 7 8 9 10 11 12
Are We There Yet?

• Industry has ultimate responsibility for the product it manufacturers
  – Some signs of newer technologies
  – Increased QbD development programs

• Why so hard to know?
  – How do you measure quality?

• What can Agency and industry do?

• FDA/CDER undertook internal assessment
Challenge in ‘Silos’

- CMC Review
- QbD
- PAT
- Facility Evaluation
Historical Focus of Staff

FDA Staffing vs. Patient Exposures

PRE-MARKET FOCUS

Years Post IND Submission:
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27

Patient Exposures:
0 2 4 6 8 10 12 14

FDA Staffing:
0 2 4 6 8 10 12 14
Concept of Operations - Structure

- Increasing complexity
- Silos
- Issues of quality

- Leverage Expertise
- Integration
- Surveillance and Metrics

Supported by holistic product quality IT data platform
Concept of Operations – Work Processes

- Individual opinion
  - Reactive; case specific

- Discipline specific viewpoint

- Standards

- Patients First
  - Incorporate QRM

Supported by holistic product quality IT data platform
OPQ Sub Office Roles (Small Molecule)

• Product Review – “What the product is and how designed”
  – Define effective clinically relevant product specifications… create standards that matter for patients

• Process/Facility Review – “How and where its made”
  – Focus on process… conduct high risk PAIs, an integrated model

• Surveillance – “How products and firms perform over lifecycle”
  – Assess and make quality visible and impactful
OFFICE OF SURVEILLANCE & QUALITY METRICS
OPQ/OS

- How the products and firms perform over the lifecycle
- Understand and assess the inventory
- Dr. Woodcock’s rallying cry…
  - How many are there
  - Where are they
  - What do they do
  - How well they do it…
- Incorporate that knowledge into our work…
  - Shortage vulnerability
  - Risk rank site inspection schedule
  - Enhanced inspection paradigm
What are Quality Metrics?

• An objective measure of the quality of a product or process
  – Quality is the fitness for intended use of the product, relevant to patients
  – Product (and/or process) segmentation

• An objective measure of the quality of a site
  – Quality is measure of site’s ability to manufacture products fit for intended use
  – Site segmentation (can include a build of product/process scores)

• An objective measure of the effectiveness of systems associated with the manufacture of pharmaceutical products, including the pharmaceutical quality system
  – On site evaluation of quality systems
More on Quality Metrics…

- Widely used in industry
  - Benchmarking database
    - Dozens of metrics
    - From ~ 600 sites
    - Common definitions
    - Potential correlations

- Components required under CGMPs
  - Annual Product Review
    - Manufacturing data, SPC charts, process capability output
  - Available to FDA Investigators during inspection

- Wide range of utility benefitting public health, industry and Agency stakeholders
Engaged Broadly w Stakeholders

• What are the right metrics?
  – Assess products
  – Assess sites
  – Assess systems

• How do we define them?

• How do we use them?

• How do we collect them (regulatory mechanism)?

• How frequently and what under what schedule?

• Which to collect and which to audit?
Quality Metrics: Industry FRN Feedback

150 Responses
1 Opposed

Responders include brand, generic, biotech, OTC, and trade/professional associations
Example: Potential Metrics Named by Stakeholders

- Batch Failure Rate
- Right First Time
- OOS / Laboratory Failure Investigation Rates

- Definitions matter!
  - Standards for sampling/acceptance plans
Example: Potential Ask of Industry

• Each FEI site (or product sponsor) reports the following (per CY) – stratify by product and/or application number (or site)
  – # of lots attempted
  – # of lots rejected
  – # of lots reworked or reprocessed
  – # of lot release tests conducted
  – # of Out of Specification Results (# of lot release tests failed)
  – # of lot release results invalidated because of laboratory error/anomaly (# of lot release test outcomes reversed due to lab error)

• Data requirements from industry are minimal
Industry Engagement
(White Papers and Conferences)

- BIO
- CHPA
- GPHA
- ISPE
- PDA
- PHRMA
- Individual Companies
Consensus Goals

• For firms, the use of quality metrics promotes responsible practices and quality driven corporate culture

• For public, a focus on quality leads to fewer recalls and quality related shortages

• For FDA, industry achieves and is rewarded for quality, without extensive regulatory oversight
Categories for “Qualifying” Metrics

• Assess sites
• Assess products
• Assess systems
• Operationalize
  – Efficiency
  – Avoid unintended consequences
• Adequacy for downgrading
Consensus Stakeholder Metrics

- Lot acceptance rate
- Product quality complaint rate
- Confirmed OOS rate
- Recall rate
Potential Gaps

- Lot acceptance rate
- Product quality complaint rate
- Confirmed OOS rate
- Recall rate

- Assess sites?
  - Are these relevant for all types of site
- Assess products
- Assess systems?
- Operationalize?
  - Potential for unintended consequences?
  - Efficiency
- Adequate for downgrading?
Ideas?

• Unconfirmed OOS rate?
  – Potentially relevant for QC labs

• Potentially expand lot acceptance rate?
  – Failures on stability
  – Media fills

• Potentially complementary metrics?
  – Right first time
  – Lot disposition rate or time
  – Yield
  – Number of products made by site

• FDA factors w/ potential utility?
  – Product type
  – Facility type
  – Establishment size
  – Time since last inspection
  – Inspection history
Conclusion

• Received significant input and support from stakeholders

• Progress on identifying potentially useful metrics and path forward

• Continued feedback welcomed
THANK YOU

Are there questions?