ENGELBERG CENTER for Health Care Reform at BROOKINGS

Measuring Pharmaceutical Quality through Manufacturing Metrics and Risk-Based Assessment

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Engelberg Center for Health Care Reform
The Brookings Institution • Washington, DC
May 1, 2014

FDA/CDER's Evolving Approach to Quality Oversight

Theresa Mullin, PhD
Director, Office of Strategic Programs
FDA Center for Drug Evaluation and Research

CDER Mission

- Promote public health by
  - Helping to ensure the availability of safe and effective drugs
  - Promoting the safe use of marketed drugs
  - Helping to ensure the quality and integrity of marketed drug products

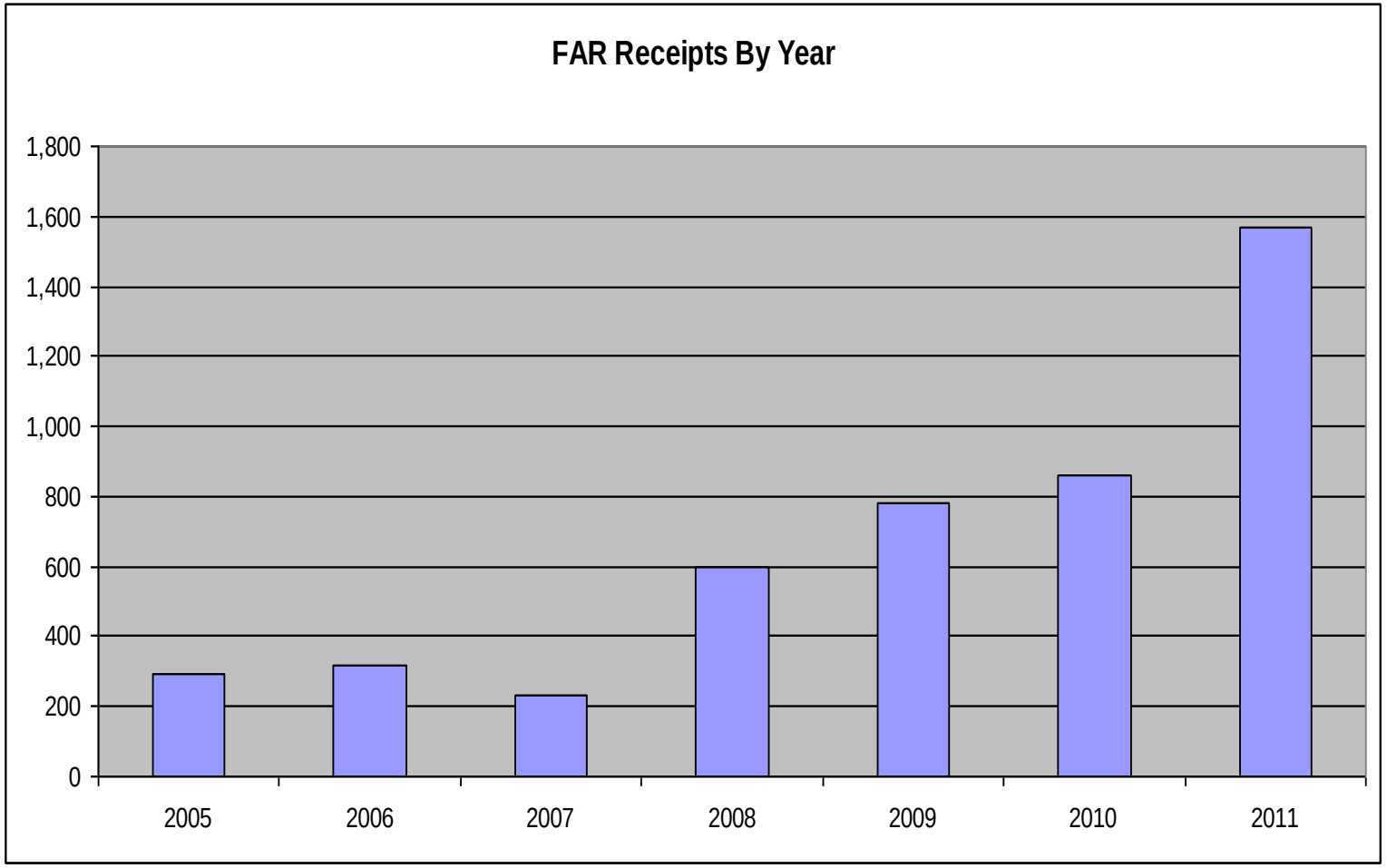
  - This includes
    - Helping expedite availability of new beneficial Rx (e.g., breakthrough drugs) and needed drugs (e.g., shortages); prevent exposure to substandard or harmful drugs
    - Clinical review results in a risk-benefit assessment
    - Need to make risk-based assessment of product quality as well

Vision for 21st Century Manufacturing

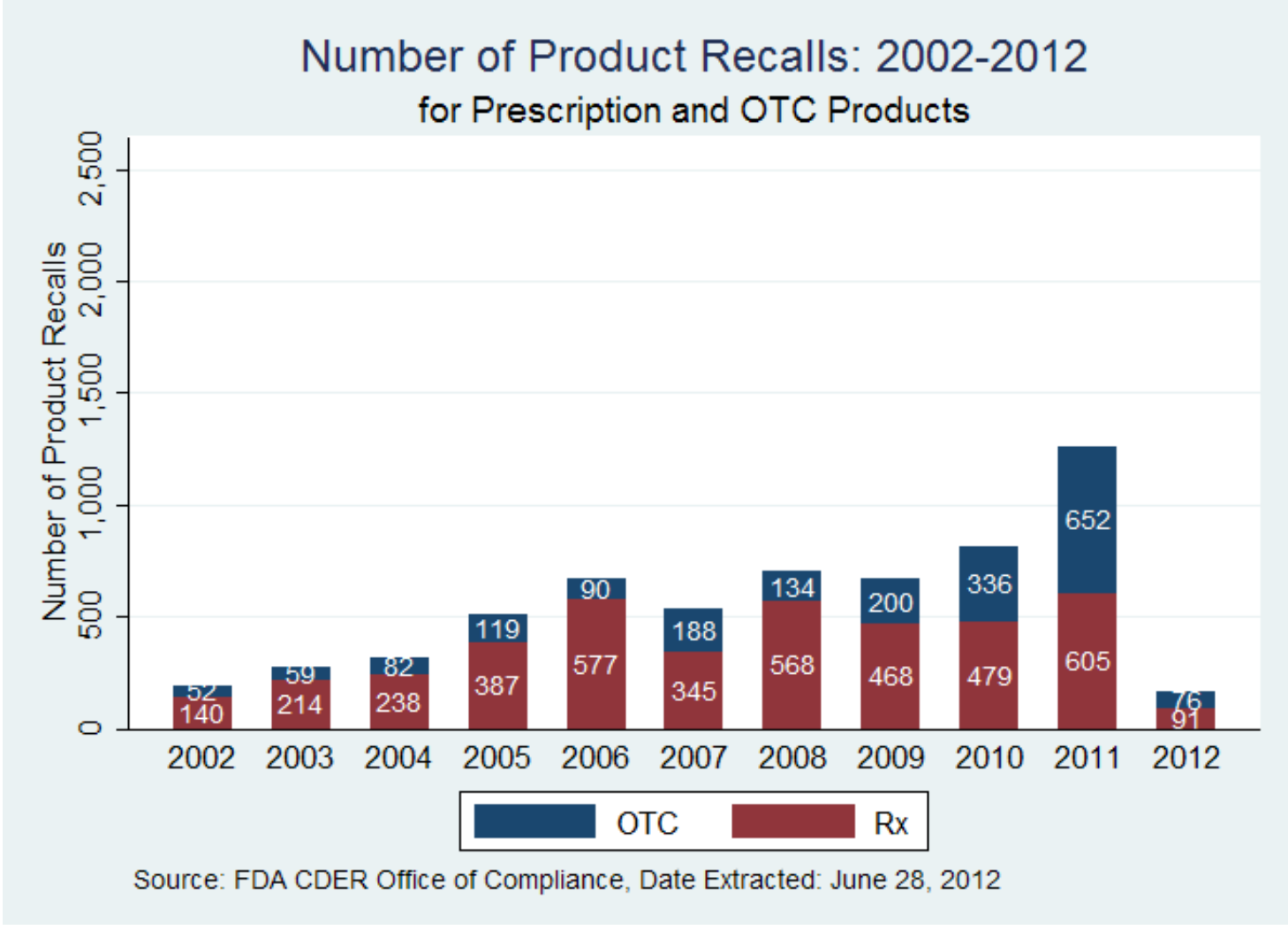
"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight."

Are we there yet?

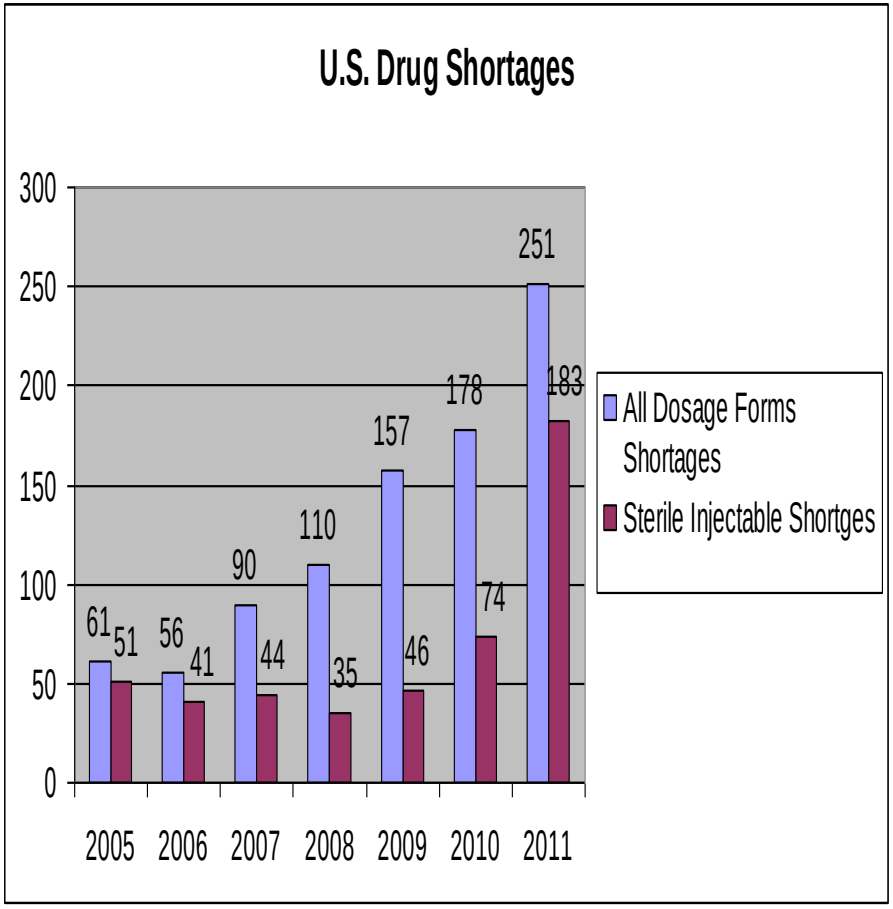
Field Alert Reports (FARs) are Increasing

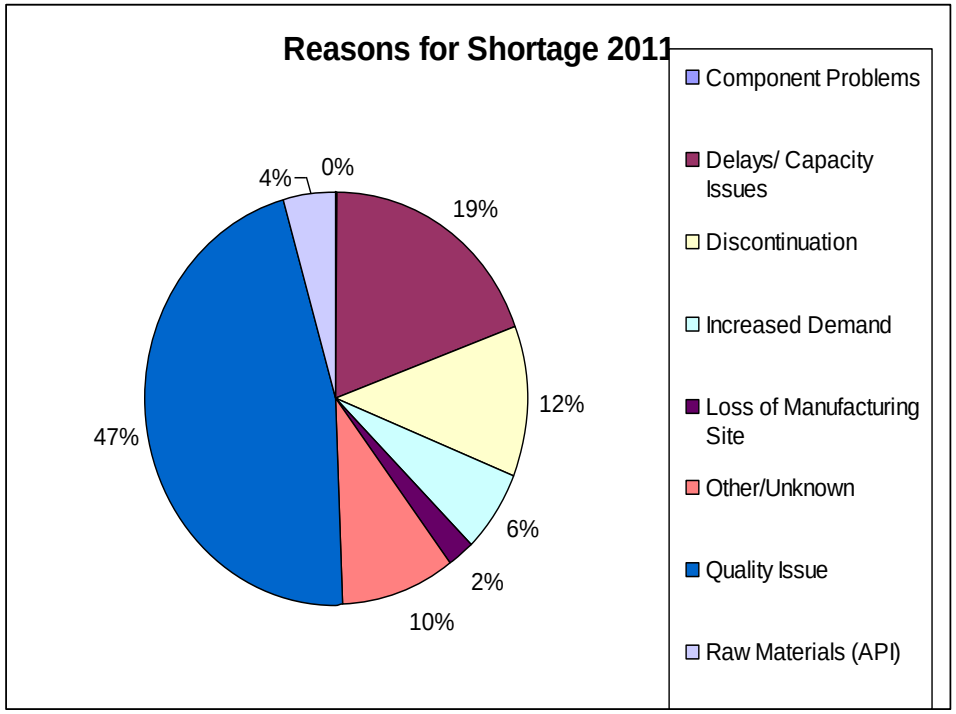


Recalls – State of Quality?



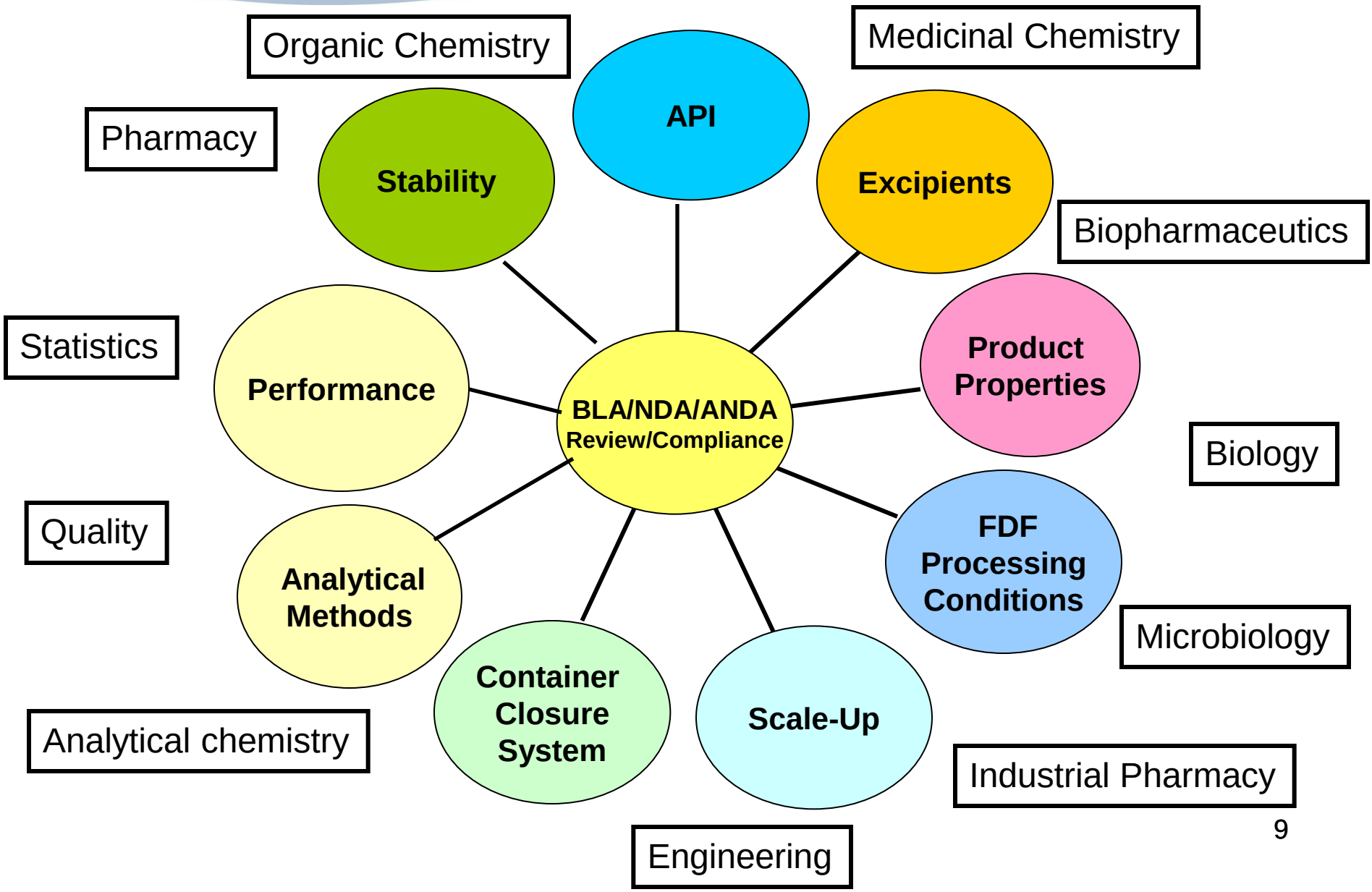
Drug Shortage – State of Quality?



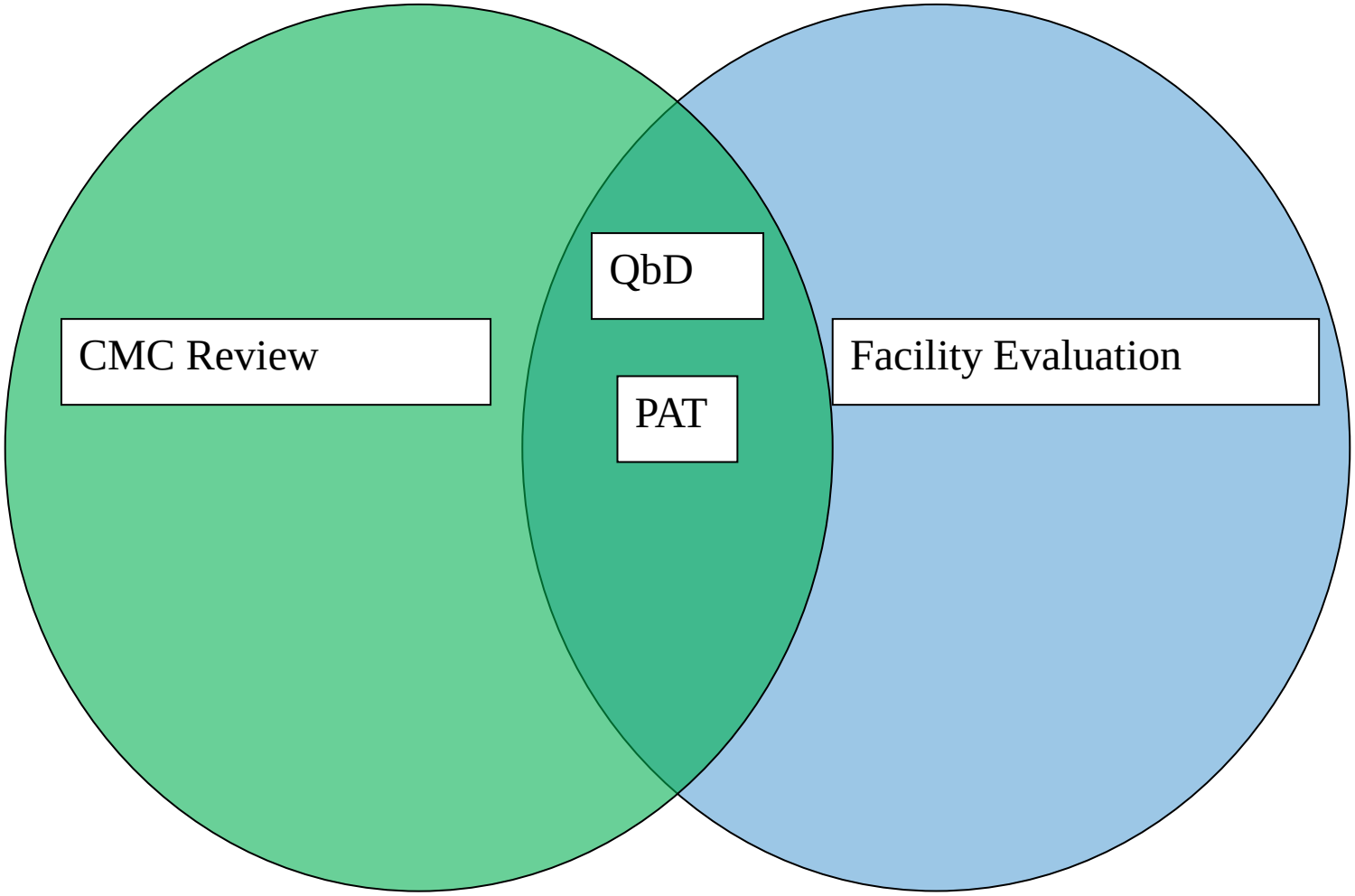


Why Are We Not There Yet?

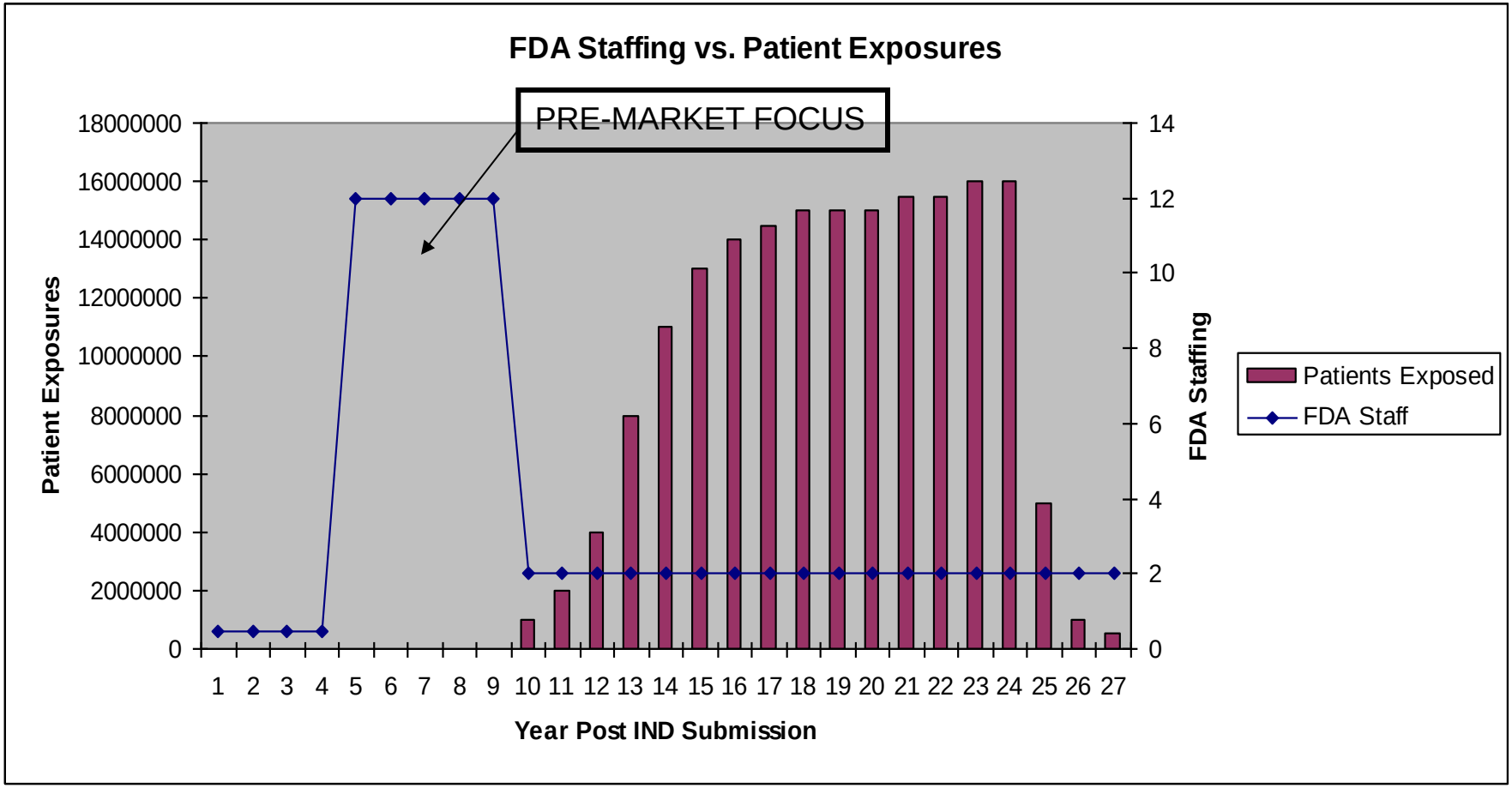
- Industry
  - Has ultimate responsibility and authority over the product it manufacturers
  - QbD should be positively impacting quality
    - QbD = Knowledge of product and process
- FDA
  - Need for integrated team-based review including all the relevant domains of scientific expertise
  - Post-market surveillance focus on cGMP deviations is not shifting drug industry's focus as needed to achieving and maintaining a state of acceptable product quality


Organic Chemistry
Medicinal Chemistry
Pharmacy
API
Stability
Excipients
Biopharmaceutics
Statistics
Performance
BLA/NDA/ANDA
Review/Compliance
Product
Properties
Biology
Quality
Analytical
Methods
FDF
Processing
Conditions
Microbiology
Container
Closure
System
Scale-Up
Analytical chemistry
Industrial Pharmacy
Engineering

Challenge in 'Silos'



Historical Focus of Staff



Fundamental Drivers of Proposed Office of Pharmaceutical Quality

- One program for drug quality across generic, brand, OTC drugs. Same quality expectations for all marketed drugs = clinical performance

- Expertise-based standards development, review and inspection, surveillance, etc., e.g.,
  - Drug synthesis
  - Manufacturing processes and facilities
  - Policy development
  - Data and surveillance
  - Evaluation

Vision for Proposed OPQ

- One Quality Voice for Drugs
  - Centralize quality drug review—creating one quality voice by integrating quality review, quality evaluation, and inspection across the product lifecycle.
- One Quality Voice for Patients-- Assure that quality medicines are available for the American public
- One Quality Voice for Industry--Establish consistent quality standards and clear expectations for industry
- One Quality Voice for Health Care Providers and Purchasers

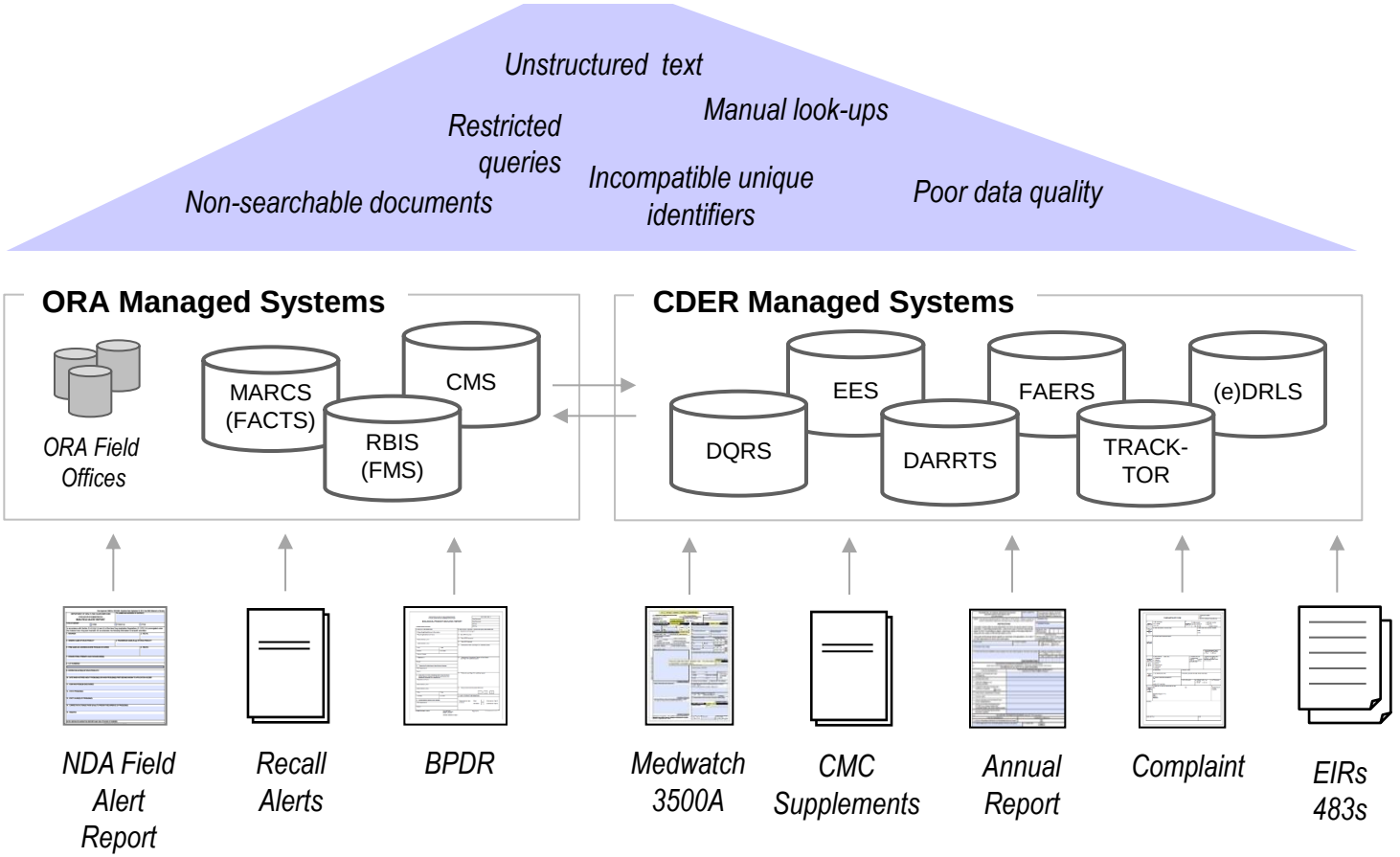
Proposed OPQ Includes an Office of Surveillance

- 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*
- Proposed Office of Surveillance will
  - Serve as business owner of quality data systems and the pharmaceutical quality platform
  - Develop and manage analytic and predictive program
  - Develop and manage new inspection paradigm and assessment program focusing on surveillance of quality

Current sources of quality information are fragmented, disparate and incompatible

What is the quality history of this sponsor, facility, or product?

What quality trends and patterns are we tracking, and what is the perceived risk?



Surveillance Incorporating Quality Metrics

What

- Objective measures of:
  - Quality of a drug product or production process
  - Quality of a site
  - Effectiveness of systems associated with the manufacture of pharmaceutical products

Why (goals)

- Induce the right behavior and responsibility for industry
  - Enable better FDA surveillance of state of the firms' quality
- Reduce product-related shortages and quality related recalls
  - Promote improved product and process capability
- Achieve product quality without extensive regulatory oversight

Quality-focused Surveillance Inspection

FDA recognizes need to expand focus of inspection beyond cGMP deviations and failures via inspection process and work product requirements

- to provide needed focus on measurement and ascertainment of the *state of quality of production and quality systems* in the inspected facility

- to support quality risk assessment and risk-based inspection as envisioned by FDASIA and required to achieve meaningful mutual reliance.

Drug Quality Surveillance Inspections

- General principles
  - Inspections should gather analyzable data where possible--to inform on-going quality assessment and “intelligence”
  - Develop standards for consistently gauging and “grading” state of quality observed by investigator, e.g., across the 6 systems*
    - Specify positive range to build on /expand on current structure of observations focused on failures and deviations
  - Develop data-rich inspection format and more structured, standardized inspection report.
    - More readily accessible, interpretable, and analyzable post-inspection, to maximize downstream use to inform FDA (and potentially other regulators)
  - End-to-end
    - pre-inspection prep through post-inspection follow-up

* Quality; materials; production; facilities and equipment; packaging and labeling; and laboratory control

We are looking forward to the next 2 days' discussion.

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Quality Metrics Update
Stakeholder Feedback, Goals, and Gaps

Russell Wesdyk
CDER/OSP
May 1, 2014

FDA Interest in Quality Metrics

- For purposes of supporting segmentation, an objective measure of the quality - fitness for intended use - of:
  - Products
  - Site
  - Quality systems
- Quality metrics are just one part of the picture
  - Intended to be enhancing FDA's analysis
  - Not replacing existing measures
- The program will likely need to learn and evolve through continuous improvement

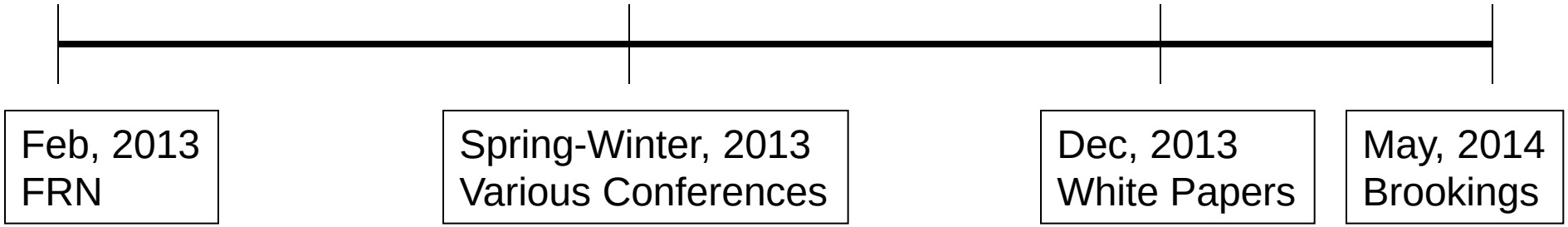
More on Quality Metrics…

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

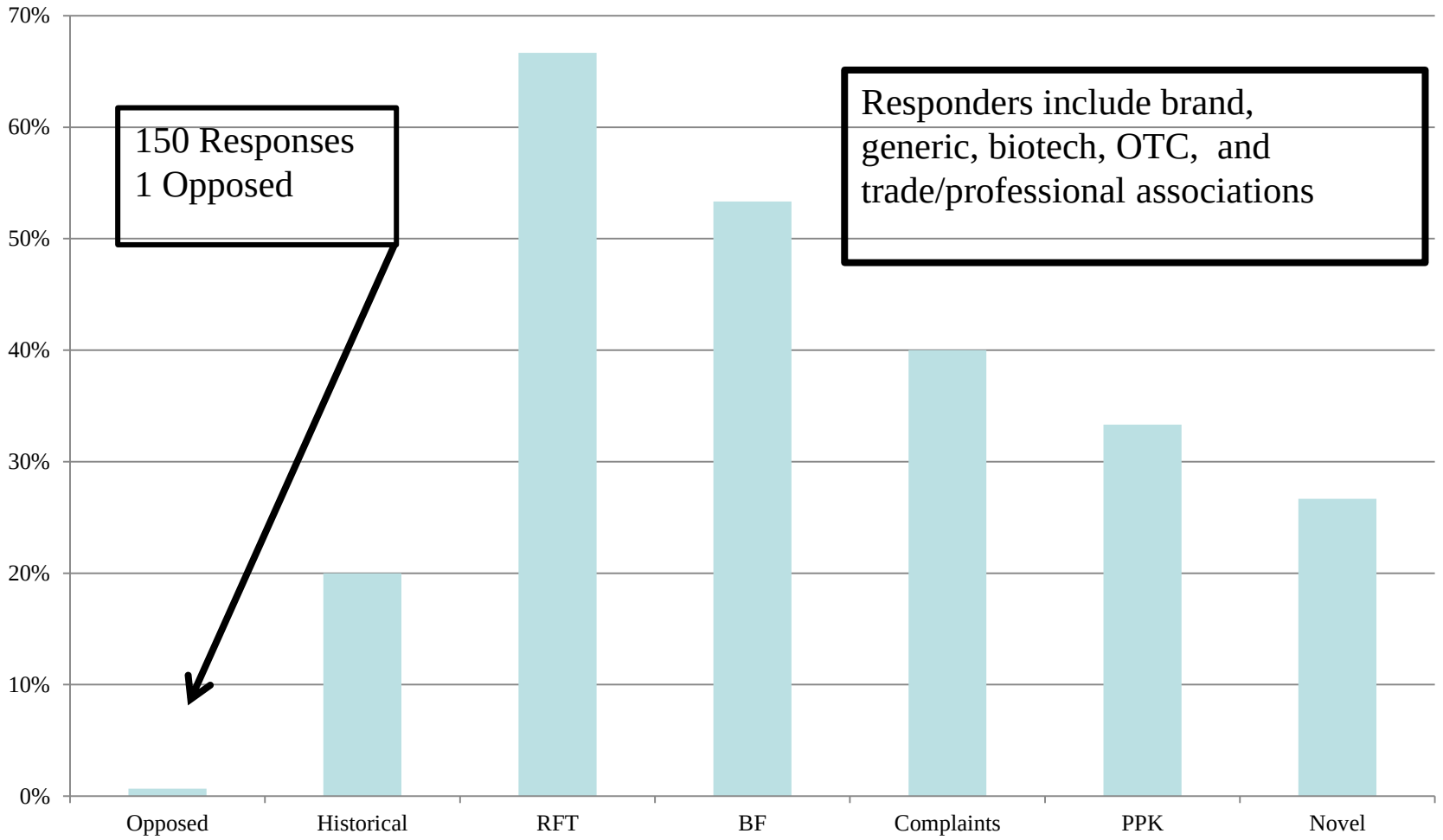
- Components required under CGMPs
  - Annual Product Review
    - Manufacturing data, SPC charts, process capability output
  - Available to FDA Investigators during inspection

- Potentially collected via FDASIA Title VII, section 706, in part to support section 705

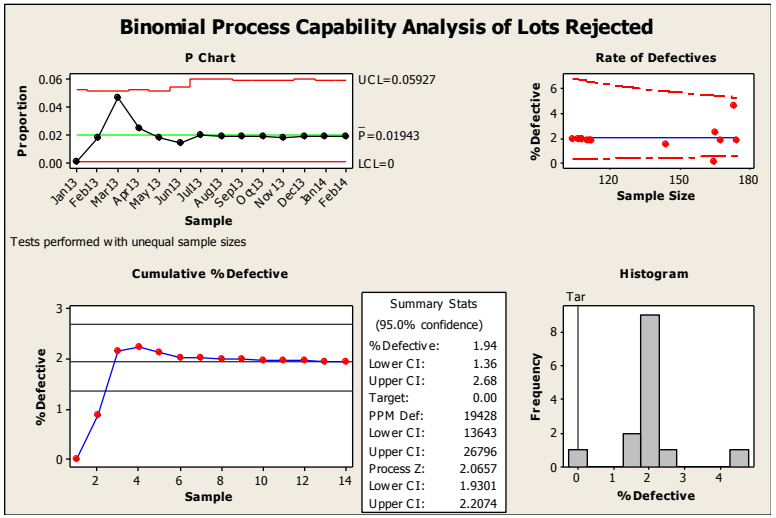
Timeline

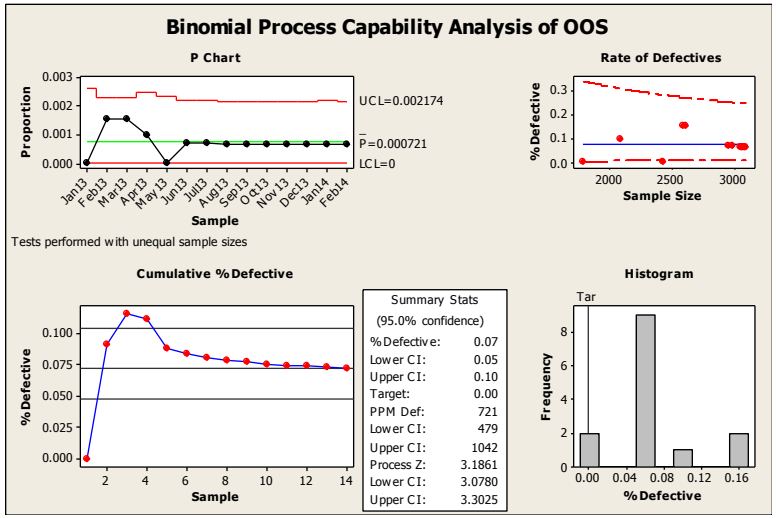

Feb, 2013
FRN
Spring-Winter, 2013
Various Conferences
Dec, 2013
White Papers
May, 2014
Brookings

Quality Metrics: Industry FRN Feedback

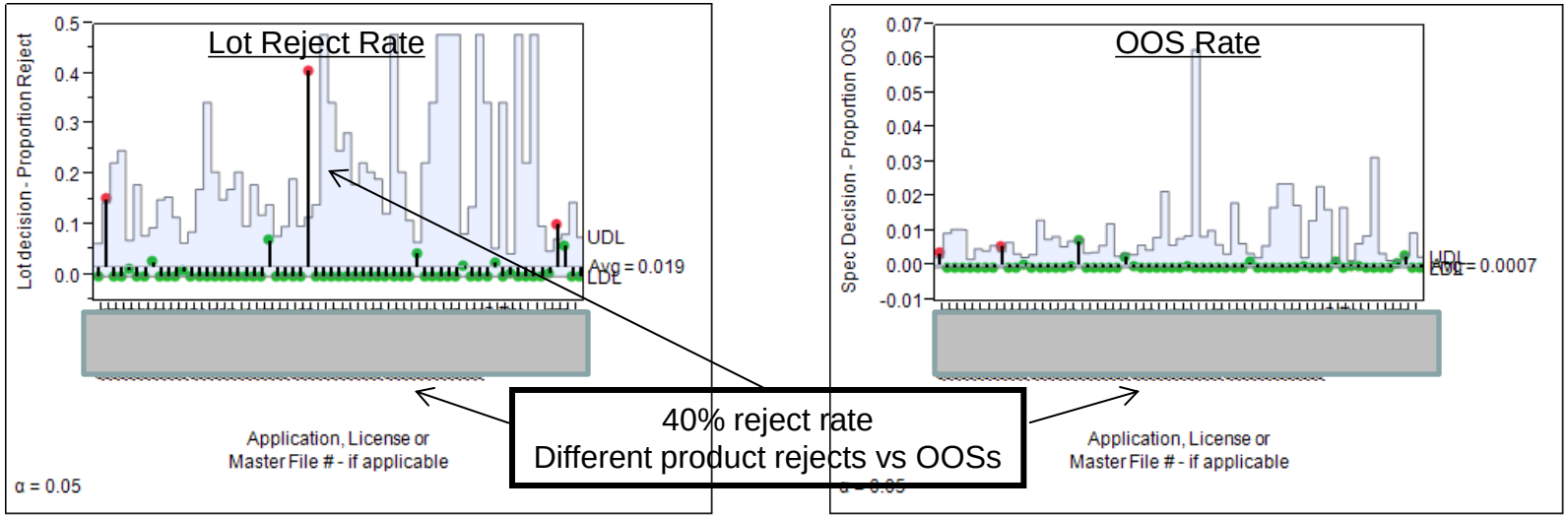


Site Monitoring





Product Comparison



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

Consensus Objectives

- Use quality metrics and other risk factors to select sites for reduced inspection frequency.
- Determine when post-market regulatory change filing requirements can be reduced for specific products, processes, or sites.
- Identify products at greatest risk of shortage and recalls.
- Use conventional and innovative quality metrics, including measures of process robustness/capability, to detect and monitor variations in product quality.
- Identify objective measures for quality system effectiveness at manufacturing sites that can underpin structured surveillance inspections.
- Use quality metrics to learn about the state of quality, establish performance goals across industry, and better communicate internally and externally.
- Operationalize the quality metrics program in a manner to that
  - minimizes potential for unintended consequences,
  - assures data integrity,
  - incorporates learning and continuous improvement, and
  - realizes efficiency, i.e., it minimizes the reporting burden on industry and the regulatory duty of FDA.

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
- OOS rate
- Recall rate

Potential Gaps

- Lot acceptance rate
- Product quality complaint rate
- 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?
- Failures on stability?

- Complementary metrics?

- Right first time?
- Lot disposition rate or time?
- Yield?
- Number of products made by site?

- Balancing metrics?

- Media Fills?
- Environmental monitoring?

- Sector specific metrics?

- Product type?
- Facility type?
- Establishment size?
- Time since last inspection?
- Inspection history?

- Some available factors?

Quality Risk Across Segments

- Generally do not see any one segment as lower risk than others
- FDASIA section 705 asks that we evaluate all segments, including OTC, in same manner
- Risk can be viewed as a function of severity and probability
  - Is exposure (distribution data) a potential component of a surrogate for severity?

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?

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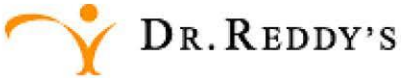
Quality Metrics: Learnings from McKinsey's "POBOS" Benchmarking

Katy George, Director
McKinsey & Company

May 1, 2014

McKinsey's "POBOS" Quality Benchmarking

- Since 2006
- 20+ companies
- 35 countries
- 140+ sites
- 100+ metrics
- Rx, Gx, OTC
- All formulations
- API and biologic drug substance

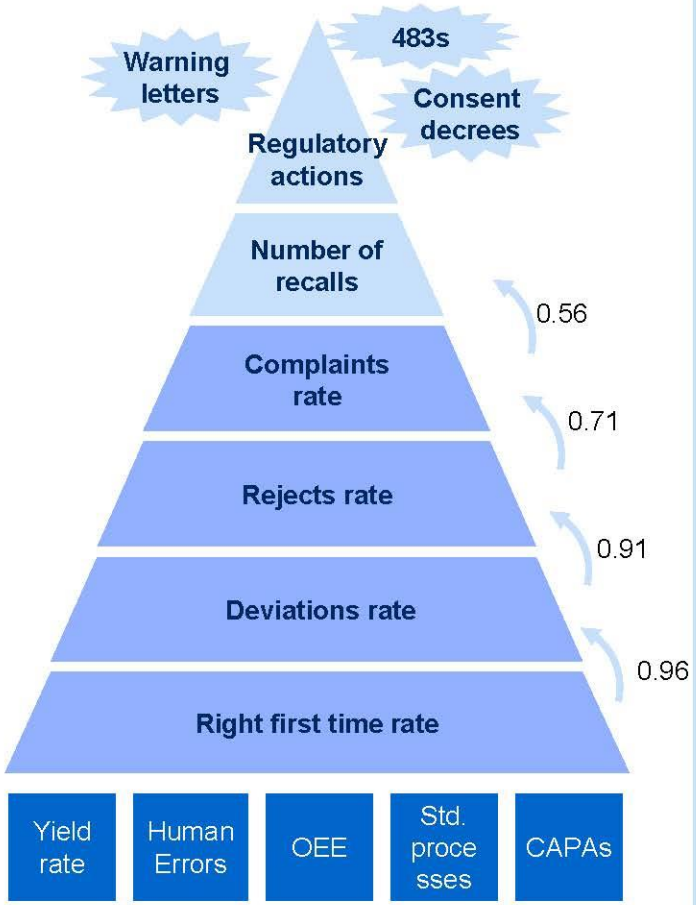


Market quality can be predicted with site-level metrics

CLIENT EXAMPLE

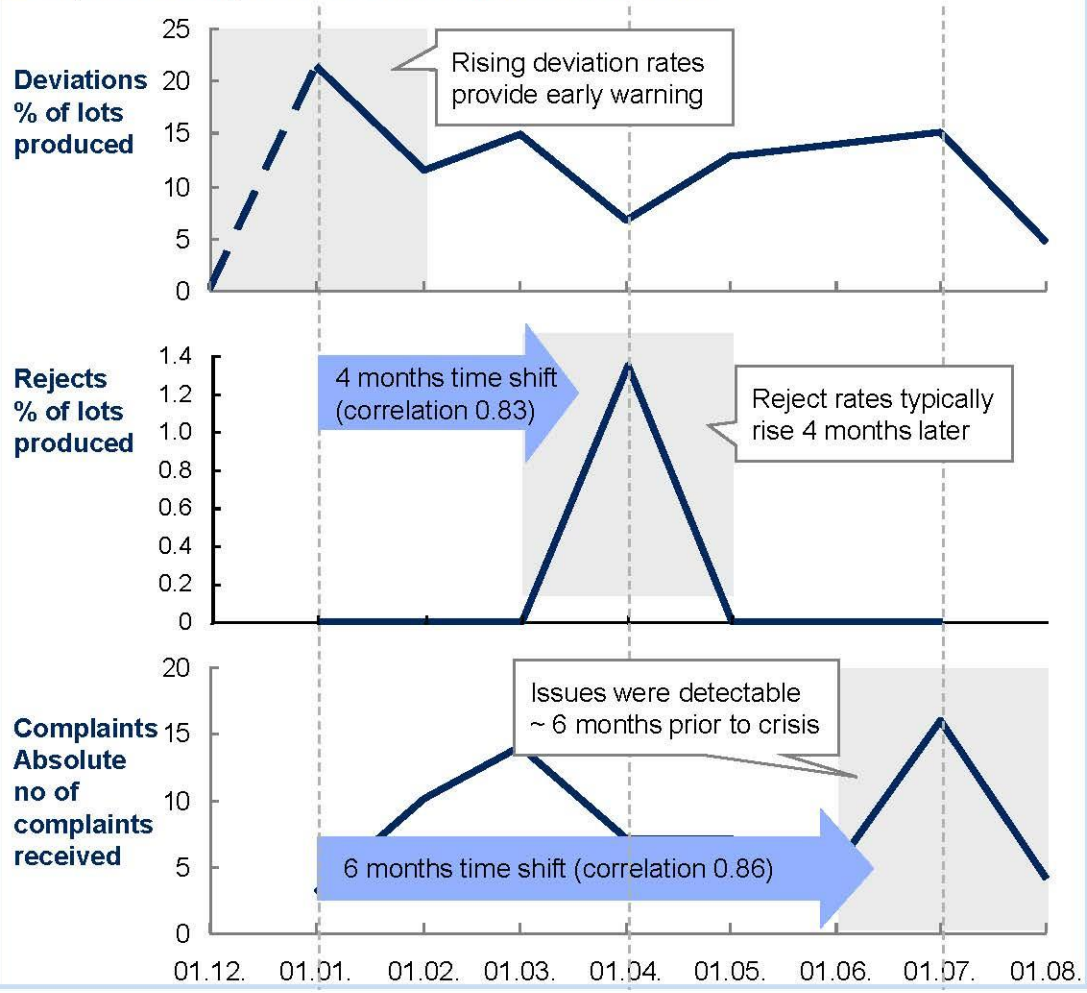
A set of leading indicators . . .

Correlation coefficients between Quality metrics[1] (perfect correlation = 1.00)



… have been shown to cascade from operations to customers

Example of Quality metrics correlation at a selected site



1 Correlation coefficients based on data samples from 14 production sites

POBOS Benchmark Database is structured around our "Quality Equation"

Quality outcomes

Quality performance

- Product quality, patient safety
- Compliance risk
- Market impact

Total Cost of Quality

- Cost of Quality systems – quality FTEs, non-quality FTEs engaged in quality, above site cost of quality
- Cost of Poor Quality

Building blocks of good quality

Operational Maturity

- Specifications integrity
- Process capability
- Operational execution

⊕

Quality System Maturity

- R&D quality
- Supplier and external manufacturers quality
- Manufacturing and quality processes
- Post-market quality

⊕

Culture and capabilities (newly added)

- Leadership and vision
- Accountability/ Ownership
- Collaboration and shared values

SOURCE: POBOS Quality

Example metrics

Quality outcomes

Quality performance

- *Complaints*
- *FDA or other regulatory observations*
- *Recalls*

Total Cost of Quality

- *Cost of Quality function*
- *Non-quality resources directed to quality activities*
- *Cost of rework and scrap*
- *Cost of recalls, Warning Letters*

Building blocks of good quality

Operational Maturity

- *# products for which CTQs are identified*
- *% QBD filed products*
- *# deviations*
- *RFT*
- *Minimum CPK*
- *Yield*

Quality System Maturity

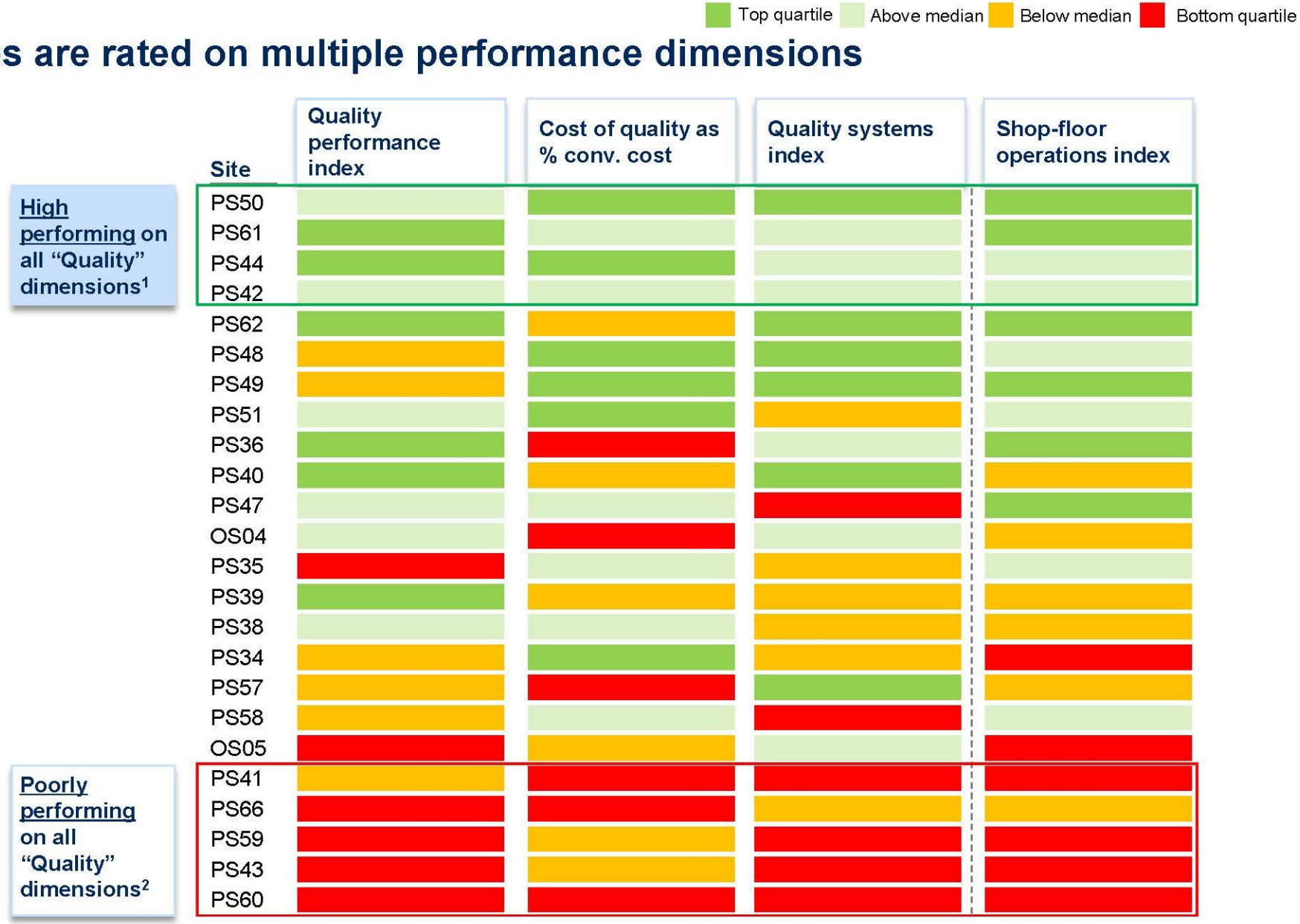
- *Preventive vs. reactive resources*
- *Supplier qualification rate*
- *CAPA closure times*
- *Recurring deviations*
- *Observations per audit*

Culture and capabilities (newly added)

- *Leadership focus*
- *Awareness*
- *Accountability*
- *Risk attitude*
- *Capabilities*

SOURCE: POBOS Quality

Sites are rated on multiple performance dimensions

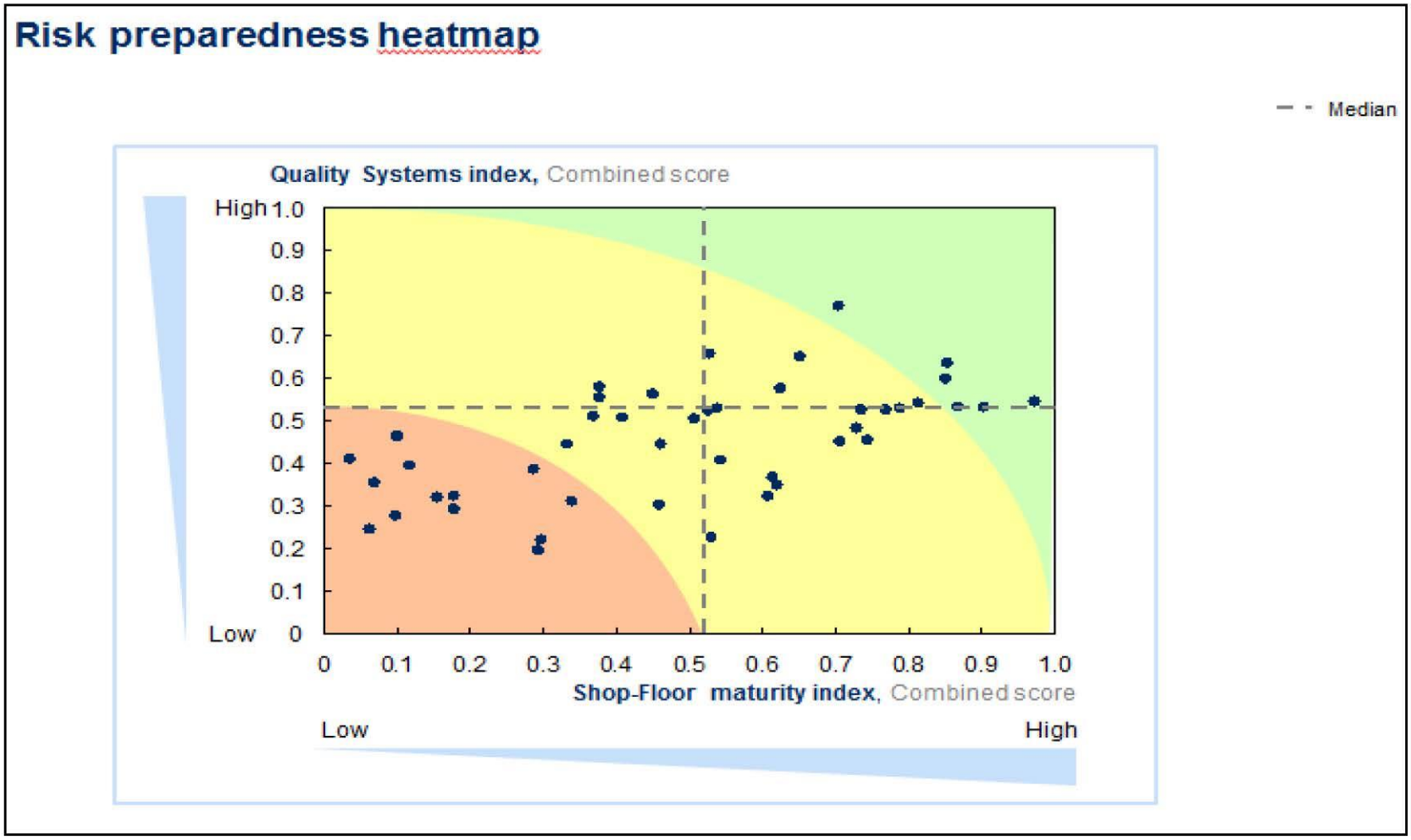


1 Better than median on all dimensions; 2 Worse than median on all dimensions

SOURCE: POBOS Quality

Companies also get a risk heatmap of their sites

EXAMPLE END PRODUCT



Source: POBOS Quality

Example learnings from POBOS Quality

1 Operations maturity and quality function effectiveness are drivers of quality performance

- Few rejects and high RFT reduce chance of recalls
- Inspection observation risk reduced through lower deviations recurrence, shorter CAPA implementation times, and more rigorous internal audits
- Fast and efficient investigations lead to fewer complaints
- Deviations increase the chance of adverse events related to manufacturing issues

2 Operational and quality system maturity can be improved

- More resources invested in prevention pay off in better operational maturity (e.g., higher RFT)
- Cross-functional involvement in quality enhances shop floor robustness, resulting in less rework
- Batch record automation reduces deviations and speeds up investigation processes; investigations automation reduces deviations recurrence
- Effective CAPAs and deadline extensions lead to fewer repeat deviations

3 Improved quality performance can lead to lower total cost of quality

- High quality performance can reduce the cost of poor quality and total quality
- Better quality performers tend to also be more efficient (both in Quality activities and for the overall plant operations)
- Higher shop floor maturity and quality system effectiveness can lead to lower quality cost

SOURCE: POBOS Quality

ISPE and McKinsey are launching a Quality Metrics pilot

Connecting a World of Pharmaceutical Knowledge

Objectives

1. **Refine** set of metrics, definition, data submission, process and evaluation. Test **mix of lagging and leading** indicators at **site and product-level**
2. **Identify applicability and methodologies** to maximize benefits for all the parties involved and create new insights
3. **Pilot** with a sample of companies and sites identified by ISPE individual members; refine methodologies over 2 periods of data collection by assessing predictive power
4. **Detail and document findings and path forward** to operationalize standard metric reporting and use of metrics in risk management

Parties to involve/ Proposed approach

- **ISPE PQLI metrics team** in collaboration with McKinsey and with input from the FDA: to design the program, its applicability for the industry and to oversee confidential evaluation of company data[1]
- **ISPE/McKinsey pilot team to work together to agree on a sampling strategy focused on small molecule solid and sterile sites.** Likely pilot design would be to start with ~15 small-molecule sites, representing both Rx and Gx. Both the ISPE recommended metrics and baselining data would be collected to enable correlation and predictive analysis. Smaller test samples from large molecule sites would be used to test the feasibility and applicability of data definitions and collection
- **McKinsey & Company** to run the overall data collection and analysis in a separate ISPE database, ensuring consistency and confidentiality among the different parties involved

1 Summary-level pilot data and analysis will be presented in aggregate to the pilot team and will be reported by technology (e.g., solid vs. sterile). Individual companies in the pilot will also be able to see their individual site data relative to the total industry sample. No individual company data will be shared with other industry members or with the FDA. Aggregate data will be blinded and shared.

SOURCE: ISPE Proposals for FDA Quality Metrics Program - Whitepaper

Backup

Complete POBOS Quality metrics list (page 1/2)

Operational maturity

Specifications integrity	▪ Number of products for which CQAs are defined ▪ % of CQA products that have CCPs tied to CQAs ▪ Average # of CQAs per products ▪ Percent of low capability processes that have CQAs and corresponding CCPs defined ▪ # of design changes in the first 6 months after product introduction
Process capability	▪ # of deviations (non-conformances) in production ▪ # of non-conformances found during incoming material inspection ▪ Percent recurring deviations ▪ Production output: w/o deviations vs. rejected vs. reworked vs. w/deviations released w/o rework
Operational execution	▪ Deviation mix by root cause ▪ Share of unit operations that have in-process testing ▪ Number of Finished product QC lab release tests ▪ Number of items in the bill of materials (BoM) ▪ % of excess materials built in in the BoM ▪ Total number of entries in a Device Master Record (DMR) ▪ Number of DMR changes in the last fiscal year ▪ Direct labor share of total ▪ For direct labor: Share of temporary FTEs ▪ For indirect labor: Breakout by job function ▪ Average tenure of permanent employees ▪ Average employee turnover ▪ Line workers per 1 supervisor ▪ % of employees that have quality targets as part of their performance review ▪ Average number of controlled documents that each operations employee needs to be trained on ▪ Age of the facility ▪ Average age of the equipment ▪ Depreciation level for facilities and equipment ▪ Capital asset reinvestment level ▪ Total spend on preventive maintenance etc. ▪ Maximum clean room rating achieved in the facility

Quality system maturity

R&D quality	▪ Number of products that underwent process or product redesign in the last 2 years to improve quality ▪ Number of deviations related to products that have their last 510k or PMA approved in the last 2 years ▪ Percent of new products that have passed pre-approval validation right-first-time
Supplier and external manufacturing quality	▪ Share of certified suppliers and contractors ▪ % of materials incoming from certified suppliers ▪ Supplier audit frequency ▪ # of suppliers disqualified in the last fiscal year for quality reasons ▪ # of suppliers "on probation" ▪ % of suppliers that have your product CQAs and have them translated into their processes with critical control points ▪ Do you assess suppliers based on their capabilities in relation to CQAs?
Manufacturing and quality processes	▪ Average time to close a deviation investigation ▪ % of investigations exceeding 45 days ▪ Share of open CAPAs that are open for longer than 1 year ▪ Total CAPA cycle time ▪ Share of CAPAs effective ▪ Number of corporate audits in the past 2 years ▪ Average days per corporate audit ▪ Number of findings from corporate audits ▪ % of findings closed on schedule ▪ Total days of audits and inspections (external or internal) ▪ Process automation
Post-market quality	▪ Average time to close a customer complaint ▪ Share of customer complaints that are older than 60 days ▪ Health authority reporting: % on-time

SOURCE: POBOS data templates,

Complete POBOS Quality metrics list (page 2/2)

Quality performance

Product quality and patients' safety

- Total number of customer complaints of that number of complaints related to new products
- Total number of MDRs and MDVs

Compliance risk

FDA:

- Number of FDA inspections at the plant in the last 3 years of them
  - number of inspections without observations
  - number of inspections resulted in a 483 form
  - number of inspections resulted in a warning letter
- Number of "for cause" inspections
- Total number of observations in 483 forms
- Total number of observations in warning letters
- Inspections by other agencies:
- Number of regulatory inspections other than FDA (e.g., Notified Body in the past 3 years (by year)
- Number of observations received from non-FDA inspections
- of that major observations\

Market impact

- Number of recall events in each of 3 last years total and by root cause
- Number of units recalled in the last 3 years
- Number of recalls of new products (launched in the last 2 years)

Total cost of quality

Cost of Quality System

- Cost of Quality function at the plant
- Of that Quality labor cost
- Average fully loaded annual FTE cost for Quality FTEs
- Above site quality function cost allocated to the plant
- Total cost of non-quality FTEs engaged in Quality activity
- Average fully loaded annual FTE cost for non-Quality FTE

Cost of poor Quality

- Bill of materials excess costs (calculated value)
- Production failure poor quality costs
  - Cost (financial value) of rejected products
  - Cost of reworked products
  - Defoa
  - Installation time/cost above standard
  - Other cost associated with production/quality failure
- Poor quality costs that become apparent through service
  - Cost of complaints
  - Warranty cost
  - Service costs (capital specific)
  - Spare parts
  - Field change orders
  - Corrective maintenance within product lifetime
- Poor quality costs generated by service:
  - Avoidable truck rolls
  - Cost of Non First Time Right (FTR) visits
  - No fault found (NFF) parts processing
- Regulatory related poor quality costs
  - Cost of recalls
  - Cost of other non-routine quality and compliance events - 483s, WL
- Fees and fines for breach of contract with clients

Revenue loss

- From non-routine quality events
- From foregone revenues due to service levels
- From competitor defections / equipment purchases

Re-source efficiency

- Allocation of quality and non-quality FTEs by activity type (used to calculate productivity)

SOURCE: POBOS data templates

McKinsey's Quality culture index compiled through employee surveys

Areas	Dimensions	Details
Leadership	Focus	Focus on ensuring compliance vs. improving and building in quality
	Direction	Stating and communicating a quality vision and policy
	Aspiration	Specific quality targets with initiatives in place to reach those targets
	Priority	Priority of quality issues when taking business decisions
	Communication	Leadership communication on the importance of quality
Mindset	Awareness	Employees' understanding of quality policies
	Accountability	Accountable and empowered employees
	Ownership	Quality and compliance as personal responsibility
	Collaboration	Quality ensured by the whole organization
Capabilities	Skills	Employees' knowledge of quality tools
	Learning	Quality training path for each employee
	Growth	Quality function rotations as part of senior management career paths
	Customers	Customer requirements for quality understanding and prioritization
Governance	Motivation	Motivating and rewarding quality performance
	Measurement	Effectiveness of quality metrics
	Reporting	Quality reporting system and issues prioritization
Risk attitude	Transparency	Understanding and managing quality risks
	Acknowledgement	Proactive identification and escalation of issues
	Responsiveness	Responding to risks
	Respect	Individual actions alignment with organization quality goals

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Quality Metrics
Discussion Set

Russell Wesdyk
CDER/OSP
May 1, 2014

Discussion Set

- Derived and built from stakeholder feedback and regulatory considerations
- An attempt to outline a potential initial metric set to meet the consensus goals and objectives
- This DOES NOT represent current or final FDA views on the topic
- It is solely intended to facilitate discussion and drive towards consensus

Discussion Set

- Describes metrics in categories
- Provides inputs and utility description
- All metrics included were taken from stakeholder feedback
- Includes potential collection approach
- Possible definitions
- Outlines sector specific environmental monitoring tracking possibility

Metric Discussion Set

Quality Metrics Discussion Set

CONFIDENTIAL AND PRELIMINARY DRAFT - NOT FOR DISTRIBUTION

Collection: *All data not available to FDA center (i.e. only available on inspection at site) to be reported annually by product sponsor. Sponsor will report by product, by site (for all approved sites), under FRN request; data portal will be available.*

Industry Consensus Metrics	Complementary Metrics	Balancing Metrics	Available Factors	Sector Specific Metrics	Inputs	API Relevance	FDF Relevance	QC Lab Relevance	Packager Relevance	Shortage Vulnerability	Leading or Lagging for Shortage
Lot Acceptance Rate				Media fill failures	# lots attempted; # lots rejected	Yes	Yes		Yes	Yes	Leading
	Stability failures				# lots studied and # tests (including all timepoints) in protocol; # of tests and lots failed	Yes	Yes			Yes	
				Environmental monitoring/bio-burden	TBD	Yes	Yes			Yes	Leading
		Right First Time Rate			# lots reworked or reprocessed	Yes	Yes			Yes	Leading
		Lot Disposition Rate or Time			# lots not receiving final disposition, or high, low, average, SD	Yes	Yes	Yes	Yes	Yes	Leading
		Lot Yield			High, low, average, and SD lot yield	Yes	Yes		Yes	Yes	
Product Quality Complaint Rate					# quality complaints; # lots released (aggregated by all sites)	Yes	Yes		Yes	Yes	
OOS Rate					# of OOS; # of release tests conducted	Yes	Yes			Yes	Leading
	Invalidated OOS Rate				# of OOS invalidated; # of release tests conducted and/or total # OOS			Yes		NA	NA
Recall Rate *(perhaps just Class I and maybe Class II but not Class III)*			Recalls/Seizures		Available	Yes	Yes		Yes	Yes	Leading
		Yes -->	Product Type		Available	Yes	Yes		Yes	NA	Static
		Yes -->	Facility Type		Available	Yes	Yes	Yes	Yes	NA	Static
			Time Since Last Inspection		Available	Yes	Yes	Yes	Yes	NA	NA
			Inspection Outcome		Available	Yes	Yes	Yes	Yes	Yes	Leading
			Establishment Size		Available	Yes	Yes	Yes	Yes	NA	Static

Category Descriptions

- Consensus
  - Majority or unanimous recommendation
- Complementary
  - Extension of consensus to achieve goals
- Balancing
  - To address gaming or unintended consequences
- Some available factors
  - Other potentially relevant factors that arose

Inputs and Utility Descriptions

- Inputs describe the data FDA would collect from firms
  - FDA does all necessary calculations to determine rates, trends, etc… where indicated/appropriate
- Relevance columns indicate when a metrics is relevant to segmenting a particular type of site
- Utility to shortage vulnerability is also noted
- Leading or lagging nature is indicated for information solely
- A lack of quality system/quality culture metrics is observed
  - An observation solely for information

Potential Collection Approach

- Potentially collect from sponsor, submitting by product
- Each product submission divided by approved sites
- Rationale is that the sponsor must also be accountable and knowledgeable for product including when out-sourcing
- Standard format and data portal could be available
- Question for consideration:
  - Should back data be requested in initial set to establish trends?

Definitions

Potential Definitions for Discussion

Batch: Specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture. [210.3]

Lot: Means a lot, or a specific portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits. [210.3]

Reprocessed: Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, and milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown the step is incomplete is not reprocessing if defined as part of the established manufacturing process. [211.115], [211.165(f)] [ICH Q7]

Reworked: Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent). [ICH Q7]

# of lots attempted: Include any lot that was attempted, even if production stopped at an in-process stage.

# of lots rejected: [211.165(f)]

Include lots that failed to meet pre-determined established (i.e. registered) product release (includes in-process specifications used later to determine release) specifications.

This does not include lots that are rejected for failing internal quality control limits.

Include lots that are rejected for any reason (e.g. deviation, error or problem).

Include lots that are deemed “partial rejections” (e.g. if a lot is produced in subparts and one or more parts fails the specification).

Environmental Monitoring

POTENTIAL ENVIRONMENTAL MONITORING/BIO-BURDEN METRICS

DISCUSSION SET

RATIONALE:

The proposal provides a high level metric to determine if the Environmental Monitoring (EM) program is functioning well. Microbiology is an inexact science and it is quite difficult to compare one firm's EM performance to another's. A firm with more hits may simply have better sampling methods. We do not want penalize those firms for better detectability, while a firm with rare hits is rewarded. There is also generally no hard spec for individual values, or definition of adverse trend (e.g., 3 out of 10 samples were contaminated), that would decisively tell us a firm's operation is out of control. So we could not create something numerical, due to the wide differences in microbial methodologies and recovery rates between facilities.

We decided that we could likely objectively measure whether the firm is performing monitoring at the critical locations, with appropriate frequency and whether they investigate when they find contamination. But the firm does need to have SOPs, meaningful limits, and investigate significant trends or action limit deviations.

PROPOSAL:

We propose to reward firms who monitor sufficiently (e.g., location, frequency, timing) and act appropriately in response to adverse trends. We propose to focus on critical surface location. We also have included a proposal for Terminal Sterilization bio-burden monitoring…

Critical Surface are "surfaces that may come into contact with or directly affect a sterilized product or its containers or closures. Critical surfaces are rendered sterile prior to the start of the manufacturing operation, and sterility is maintained throughout processing."

POTENTIAL METRICS:

Critical Surfaces

Does EM program for each processing line include a daily sample of critical surfaces on each processing line? Y/N

Is air monitored during each shift for each line? Y/N

Are personnel samples obtained for each operator in association with each operation? Y/N

If not, identify the processing lines and identify which aseptic processing line lacks this type of EM sampling.

THANK YOU

Are there questions?

ENGELBERG CENTER for Health Care Reform at BROOKINGS

Measuring Pharmaceutical Quality through Manufacturing Metrics and Risk-Based Assessment

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