Connecting People, Science and Regulation

Quality Culture

Update for NE Chapter

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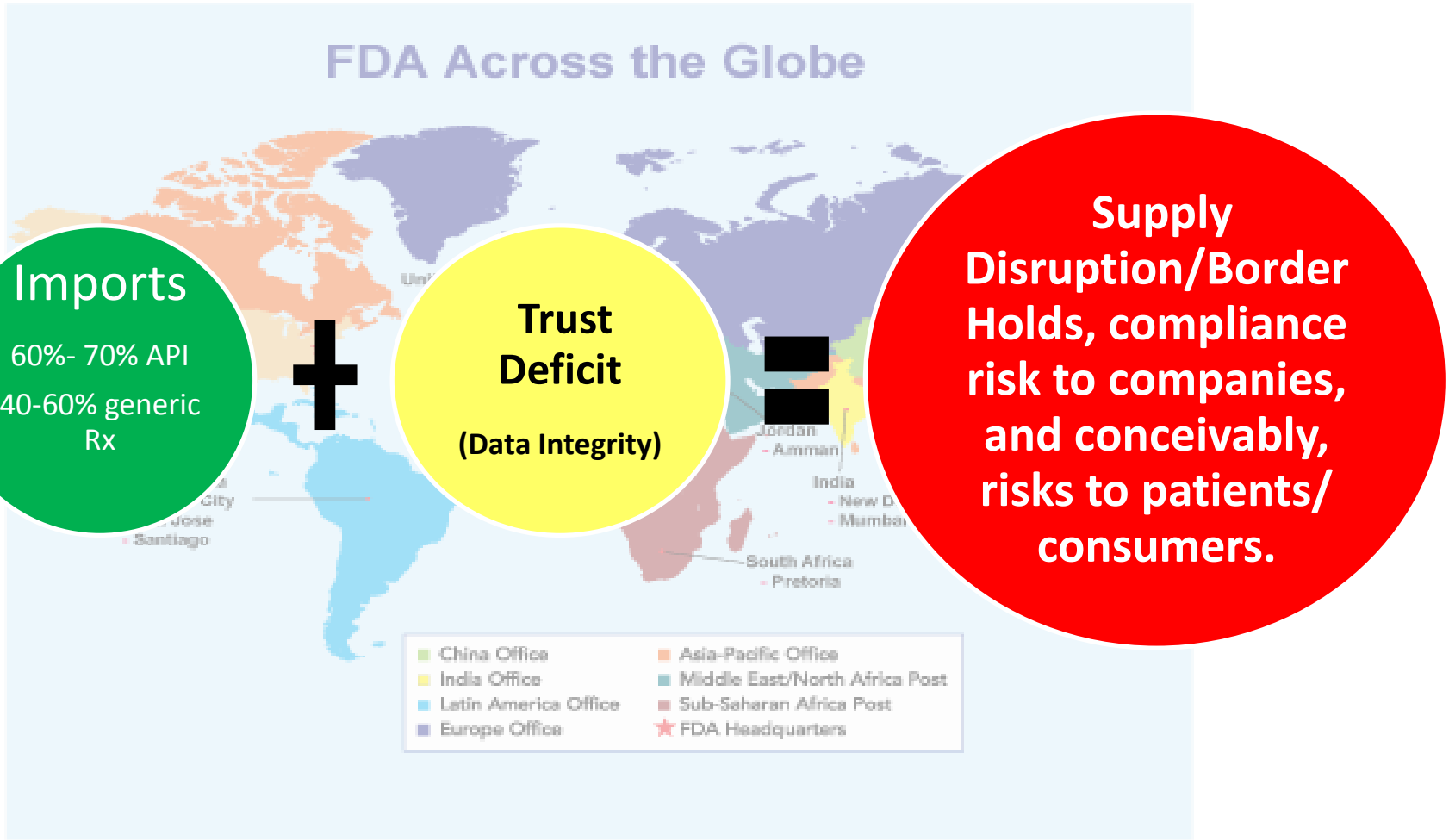
Why is Quality Culture so hot now….

- The FDA Quality Metrics initiative has raised questions about the role of quality culture in driving behaviors vis-à-vis metrics collection and decision making.
- Recent rash of Data Integrity problems discovered by regulators
  - FDA (15 WL's), EMA (1) and WHO (1)
  - Pharmaceutical Companies in India (12); China (1)
    Canada (1); Italy (1); Mexico (1); US (1)
  - Computer data acquisition systems & audit trail

Quality Culture in a Globalized Supply Chain



Agenda

- Multicenter Data Integrity Workshop in India: Hosted by US FDA and EDQM
  - Data Integrity & Fraud
  - Case studies that reflect Quality Culture

- Quality Culture Metrics Survey
  - Progress to date

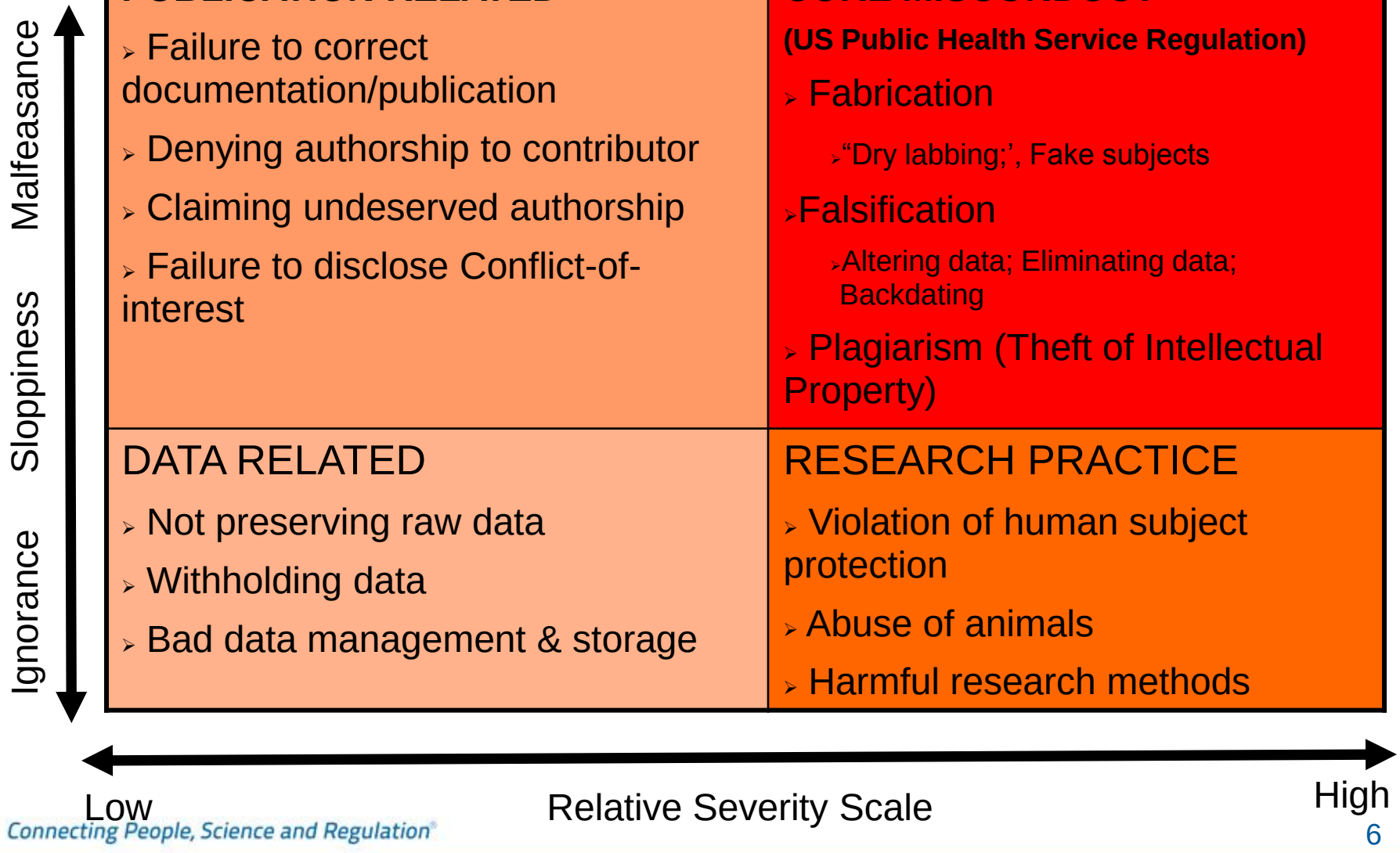
Data Integrity & Fraud: The Misconduct Scale

Innocent Ignorance	Surprising Sloppiness	Malicious Malfeasance
Misconduct of uninformed kind	Misconduct of lazy kind	Misconduct of sleazy kind
Act is unintentional; Non-Compliance is unintentional	Act may or may not be intentional; Non-compliance is unintentional	Act is intentional; Non-compliance is intentional
Discarding source documents after accurate transcription; Deleting e-files after printing	Inaction, inattention to detail, inadequate staff, lack of supervision	Data manipulation, data falsification, mis-representation, with holding critical information

Misconduct does not include honest error or honest difference of opinion.

Adapted From: Misconduct in Research- Innocent Ignorance or Malicious Malfeasance; Stan W Woollen, Biomonitoring Program, FDA

Types of Scientific/Technical Misconduct

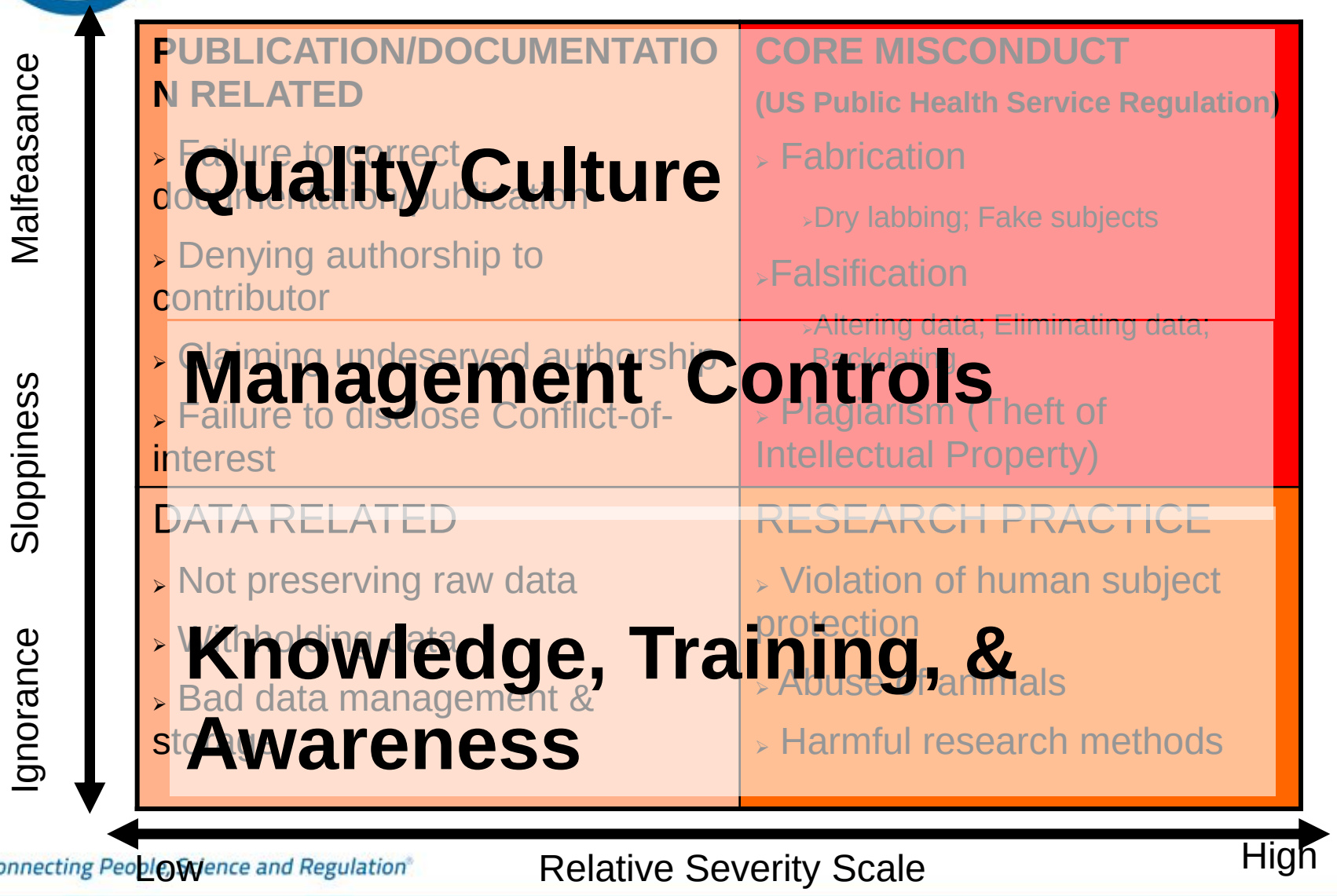


Motive & Intent

Ignorance & Sloppiness		Fraud
Not pre**se**rving data	→	Eliminating or destroying data
Omission of data	→	Withholding data
Over writing e-data or inappropriate IT system configuration	→	Intentional Deleting e-files

It is very important to determine whether there is motive and or intent to deceive.

Types of Scientific/Technical Misconduct



Motives or Risk Factors for Fraud

Misconduct cases are predominantly driven by Individual self Interest

- Were under career pressure
- Knew, or thought they knew what the answer would turn out to be if they went to all the trouble of doing the work properly, and
- Were working in a field where individual experiments/tests are not expected to be precisely reproducible.

Ref: David Goodstein, Caltech; Conduct and Misconduct in Science
<http://www.physics.ohio-state.edu/~wilkins/onepage/conduct.html>
[Tuesday, 28-Jan-2014 17:30:15 EST]
Edited by: wilkins@mps.ohio-state.edu on Monday, 15-Jan-2001 14:29:13 EST

- Were under financial pressure/ greed

Seven Elements of an Effective Compliance Program

Malfeasance

Sloppiness

Ignorance

- **Reporting-\ Speak Up & Voluntary Disclosure**
- **Enforcement & Discipline**
- Oversight - Compliance Committee
- **Auditing & Monitoring**
- **Response & Prevention**
- Standards and Procedures
- Education and Training

Culture

Controls

Knowledge

Compliance Program Guidance to Pharmaceutical Manufacturers; April 2003
Office of Inspector General
Health & Human Services, Unites States

What is Culture ?

- The collective pattern of beliefs, values and expectations.
- Observable Actions and Behaviors
- Unwritten rules – “the way we do things around here”
- **Culture and leadership are interdependent.** Senior leaders say, do and reward behaviors that create culture and allow for or derail successful implementation of change.

Compliance Program Guidance to Pharmaceutical Manufacturers

The Office of Inspector General recognizes that the implementation of a compliance program may not entirely eliminate improper conduct from the operations of a pharmaceutical manufacturer. However, a good faith effort by the company to comply with applicable statutes and regulations as well as federal health care program requirements, demonstrated by an effective compliance program, significantly reduces the risk of unlawful conduct and any penalties that result from such behavior.

Compliance Program Guidance to Pharmaceutical Manufacturers; April 2003
Office of Inspector General
Health & Human Services, Unites States

Disclaimer

The following Case Studies are fictionalized versions based on real life scenarios . Any resemblance to persons living or dead, or companies still operating, closed or merged is purely coincidental.

Case Study 1

Too Embarrassed to Act

Loop Holes in HPLC Data Acquisition System- Security Resulting in Dry Labbing

Learning Goal:

- Interview Tactics Used
- Importance of Swift Actions
- Importance of Communication Strategy

Case Background

- A QC Chemist running an HPLC assay in 2003 for potency for a high volume product, noticed the peak height of one of the batches was atypically low indicating a potency of about 75%.
- The chemist re-injected the same sample prep, and again got low results (about 75% potency)
- The chemist followed OOS investigation procedure, checked results for other tests completed for the batch (Dissolution Test completed by another chemist). The batch had met dissolution thereby contradicting the potency result. The chemist repeated the potency test in triplicate and got 75% potency again.
- Dissolution test was repeated and failed.
- OOS Investigation could not find a laboratory cause, manufacturing investigation uncovered 1 of 4 API canisters weighed was not added

Case Background (contd).

- Change of focus of OOS investigation from 75% potency to acceptable dissolution test. Chemist 2 claimed dissolution sample switched inadvertently.
- One Supervisor suspected fraud contacted management and HR. Management discussed the issue in staff meeting. Agreed this was serious Non-conformance aged for 3 months, chemist counseled to be more careful in labeling samples, Non-Conformance closed.
- Anonymous individual reported concern through hotline and also called company's compliance office.
- Special investigators visited site within 24 hours and confirmed incident, NDA Field Alert issued resulting in 5 investigators from FDA within 2 hours of reporting incident.
- Since Firm had voluntarily disclosed issue and started Independent Investigation FDA agreed to give the firm a chance to complete the independent investigation and report findings. Two FDA Investigators stayed at plant and started GMP Inspections of areas other than lab.

Case Investigation & Communication Strategy

- **Establish Dissolution Test was performed by reviewing instrument logs, facility and laboratory badge access, and data acquisition system login**
- Find the chromatogram and Injection with 75% peak height
  - Audit trail
  - Nightly Server back-up
- Interview each chemist individually in presence of employment attorney– Confront with available evidence and statement made by co-workers. Maintain anonymity of information obtained.
  - Interview investigation targets as well as individuals who were not targets but could provide evidence and/or insight
  - Interview management
- Provide updates to Regulators and Company Executive Management

Investigation Findings

- A temporary Chemist from staffing agency found a way to rename data files using Windows OS function
- Data acquisition system audit trail could not track changes made using Windows commands
- Five other temporary chemists, two regular chemists, and one supervisor were aware of the loop hole.
- Temporary chemist was considered a ‘Star’ for being productive and efficient,
- Over 500 batches potentially affected
- Site QA Management was not decisive immediately after 75% potent batch was discovered this sent wrong message to the chemist involved.
  - Temporary chemists believed practice was condoned.
- Site Management did not escalate the matter
- Too many system super users

Company Actions Depicting Culture

- Disciplinary Actions To Set Tone
  - Terminations: Chemists, Supervisor, and Laboratory Director
  - Voluntary Separation: Site Compliance Director & Site Quality Director
  - Resignation: Quality Vice President
- Commitment to Regulators
  - Lesson learned training to all laboratory personnel globally
  - Share lessons learned with regulators
  - Share information on Lab System Security and audit trail at an Industry Meeting
- Commitment to Fix System
  - Audit trail on servers and work with system vendor to fix problem

Are the actions taken adequate to establish a good Quality Culture?

Case Study 2

No Win Position

Raw data on scrap pieces of paper and written on hand

Learning Goal:

- Getting to root cause

Case Background

- Company auditor found scrap of paper in waste basket with numbers scribbled.
- Interviews with laboratory personnel and laboratory supervisor established numbers were pH data.
- Similar incident was noted in an audit 2 years earlier. Chemist was terminated.
- Supervisor informed auditor of zero tolerance policy and chemist will be terminated

Investigation Findings

- The repeat incidents occurred in one specific lab and involved the same product.
- Incident occurred despite training of lab personnel on good documentation practices
- Product being tested was not buffered, and the PH meter would not stabilize easily.
- Results in spec or OOS would depend on moment data recorded
- Formulation scientists were aware of problem but blamed QC chemist

Company Actions Depicting Culture

- Was termination of the two chemists appropriate?
- Did lab management get to true root cause?
- What do the actions say about Quality Culture

Case Study 3

Covering for the team

Signing for another employee

Learning Goal:

- Understanding your operations
- Importance of a speak-up culture
- Getting to root cause

Case Background

- QA batch record reviewer noticed initials of employees working in aseptic filling room did not match initials of operators on record.
- All employees were trained on documentation practices and SOP specifically prohibited employees initialing documents as another employee.
- SOP for interventions during filling required each operator to enter activity performed.
- In case of line jam, one operator standing by the control panel would stop the line, and another operator standing by the line would remove jammed vials using aseptic technique.
- Per procedure, each operator was required to document their activity

Investigation Findings

- QA investigation revealed the initials did not match because a operator had entered a co-workers initials besides task performed using the co-workers nick name

- During investigation interview, operator acknowledged he signed for his co-worker and rationalized that it was too burdensome for his co-worker to leave his work station and make entries in the batch record.
- Operator also rationalized that if he did not document, most probably his co-worker would not document his actions.

mpany Actions Depicting Culture

- Is termination of the operator appropriate action?
- What additional actions should the company take?
- What do the actions say about the company culture ?

PDA Quality Culture Survey

The first of it's kind in our Industry

PDA Hypotheses

- The Quality Culture of an organization is directly linked to its ability to produce high quality products and patient outcomes. Compliance metrics alone are not sufficient.
- Quality Culture Management (Maturity) Attribute metrics are the Surrogate for Quality Culture behaviors.
- Quality Culture Management (Maturity) Attribute metrics can differentiate site Quality Culture behaviors.

Problem Statement

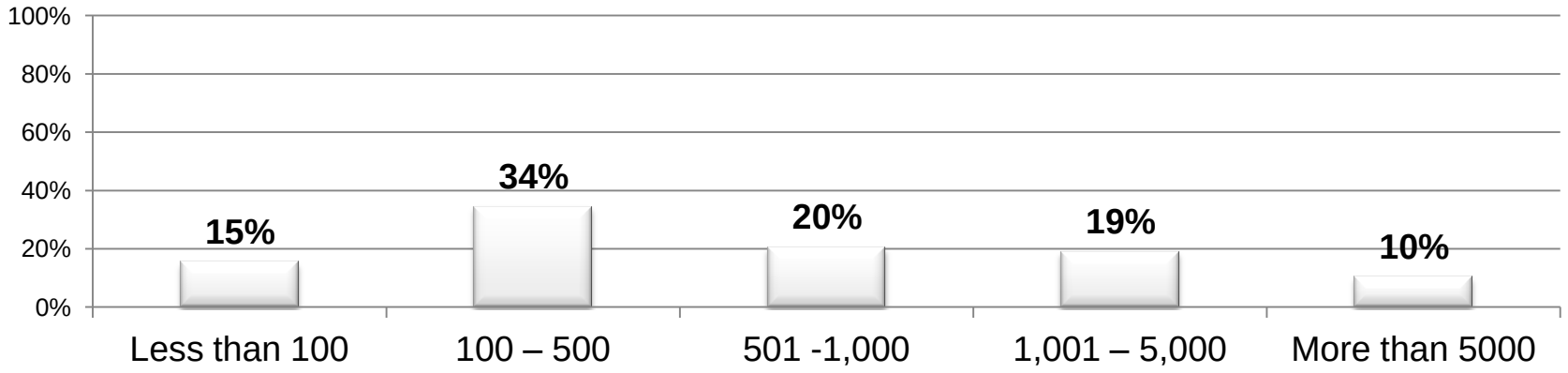
- Is there a surrogate measurement for Quality Culture that is objective and verifiable?
  - Culture is made up of behaviors but also values, beliefs, attitudes, and governance.
  - Quality Culture is a subjective measurement at best.
  - PDA Survey attempts to find and evaluate the strength of relationships between Quality Culture Behaviors and Quality Culture Management & Maturity attributes

Survey Structure

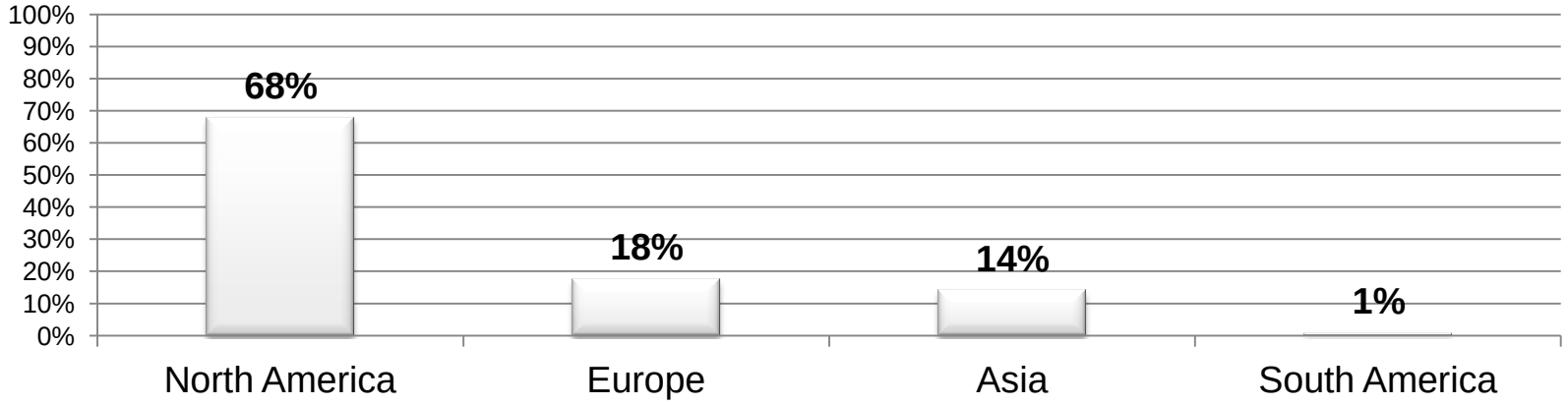
- Section A: Demographics
  - Primary business of products manufactured
  - Primary class of product manufactured
  - Primary type of product manufactured
  - Employees at Site
  - Location of site
  - Organization of responder
  - Management / Non Management
  - Question for Consultants to rate “majority of my clients”

Demographic Results

Number of Employees at Your Site



Location of Your Site



Survey Structure (cont.)

- Section B Quality Culture Behavior Categories
  - Communication / Transparency
  - Commitment & Engagement
  - Technical Excellence
  - Standardization of Criteria or Requirements
  - Reward and Recognitions
  - Speak up for Quality Culture
- Observed Behaviors in Management and Co-workers separately
- Question 25 asks the type of Quality Culture metrics the site uses

Survey Structure (cont.)

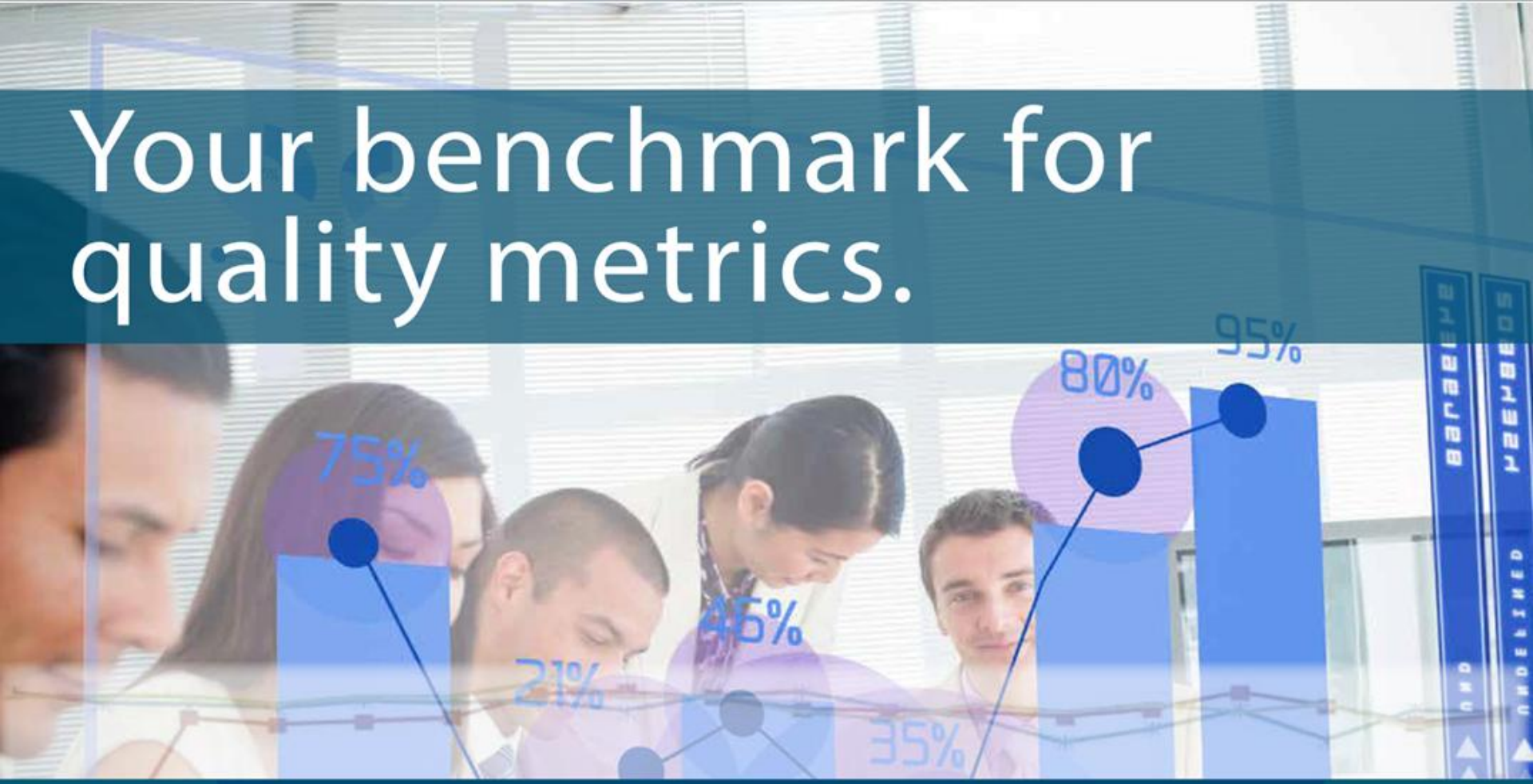
- Section C Quality System Maturity Categories
  - Prevention Program
  - Quality Management and Issue Escalation
  - Training and Personnel Development
  - Quality System Management
  - People and Communication
  - Continuous Improvement

Further Analyses Planned

- Calculate Aggregate Behavior and Management/Maturity Scores
- Identify Behavior Categories that effect Management/Maturity Score
- Identify Individual Behavior Attributes within Categories that effect Management/Maturity Score
- Identify Management/Maturity Attributes that effect Behavior Scores

Results To Be Presented and Discussed
2014 PDA Pharmaceutical Quality Metrics Conference
December 2-4 Washington, D.C.

Your benchmark for quality metrics.



2014 PDA Pharmaceutical Quality Metrics Conference

Exploring Quality Culture and Quality Systems Maturity

PDA
Parenteral Drug Association

December 2-4, 2014
Omni Shoreham Hotel, Washington DC
Exhibition: December 2-3 Course: December 5

www.pda.org/metrics2014
#PDAMetrics2014