XAVIER HEALTH

The World of Quality Metrics

Metrics Activity and Outcomes for Pharma and Device

Association of Food & Drug Officials
AFDO
Founded 1896

June 27, 2016

Xavier Device and Pharma Initiatives

Diversity in:

- Company size
- Type of company
- Management level
- Functional area
- Years of experience

Device Team Members (1 of 5)

First	Last	Company
Paul	Andreassi	Fisher & Paykel Healthcare
Karen	Archdeacon	FDA
Pat	Baird	Baxter Healthcare
Kathy	Bardwell	Steris
Anupam	Bedi	AtriCure
Pankit	Bhalodia	PwC
Kankshit	Bheda	PwC
Steve	Binion	BD
Robin	Blankenbaker	W.L. Gore & Associates
Rafael	Bonilla	ScottCare
Gina	Brackett	FDA
Kate	Cadorette	Steris

Device Team Members (2 of 5)

First	Last	Company
Patrick	Caines	Baxter Healthcare
Tony	Carr	Boston Scientific
Kara	Carter	Abbott Vascular Division
Vizma	Carver	Carver Global Health
Ryan	Eavey	Stryker
Joanna	Engelke	Boston Scientific
Tom	Haueter	Clinical Innovations
Chris	Hoag	Stryker
Jeff	Ireland	Medtronic

Device Team Members (3 of 5)

First	Last	Company
Frank	Johnston	BD
Greg	Jones	BSI
Bryan	Knecht	AtriCure
Jonathan	Lee	PwC
Bill	MacFarland	FDA
Kristin	McNamara	FDA
Rhonda	Mecl	FDA
Brian	Motter	J&J MD&D
Ravi	Nabar	Philips

Device Team Members (4 of 5)

First	Last	Company
Steven	Niedelman	King & Spalding LLP
Scott	Nichols	FDA
Pete	Palermo	CR Bard
Luann	Pendy	Medtronic
Marla	Phillips	Xavier University
Greg	Pierce	Engisystems
Susan	Rolih	Meridian Bioscience, Inc.
Barbara	Ruff	Zimmer Biomet
Joe	Sapiente	Medtronic
Gin	Schulz	CR Bard
Benjamin	Smith	Biomerieux

Device Team Members (5 of 5)

First	Last	Company
Isabel	Tejero	FDA
Shelley	Turcotte	DePuy Synthes
Sam	Venugopal	PwC
Marta	Villarraga	Exponent
Monica	Wilkins	Abbott

46 Members

Pharma Team Members (1 of 3)

First	Last	Company
Dee	Ableha	BMS
Martyn	Becker	Martyn Becker Assoc.
Grace	Breen	Impax
Brian	Carlin	FMC
Patrick	Crowley	Callum Consultancy
James	Horger	Mallinckrodt
Joanne	Humble	Catalent
Sharon	Johnson	Catalent
Dan	Jordan	Shire
Anil	Kane	Patheon
Kristina	Kucharski	United Cargo

Pharma Team Members (2 of 3)

First	Last	Company
Ben	Locwin	Biogen Idec
Kim	Mandrell	Mallinckrodt
Mike	Markham	Aptalis
Sean	McCrossen	IEXA100 Consulting
Andrew	McNicoll	Patheon
Joseph	Northington	Purdue Pharma
Hank	Nowak	Patheon
Christophe	Pamelard	Purdue Pharma
Nathan	Parker	Cook Pharma
Marla	Phillips	Xavier University
Peter	Pitts	Center For Medicine

Pharma Team Members (3 of 3)

First	Last	Company
Anil	Rattan	Shire
Kathy	Regelski	Aptalis
Prakash	Savarirayan	Shire
Kevin	Slatkavitz	ThinkQuality
Jack	Solomon	Core Risks
Sam	Venugopal	PwC
Jamie	Wilson	Navidea
Louis	Yu	Perrigo
Greg	Yurchak	RightSourceRX
Bob	Zinser	Patheon

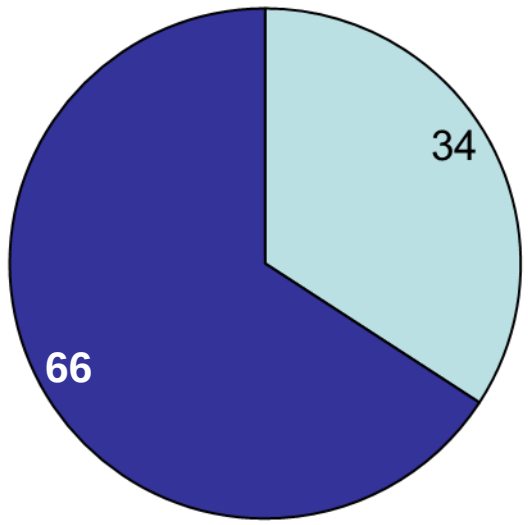
32 Members

Why is there so much Attention on Metrics?

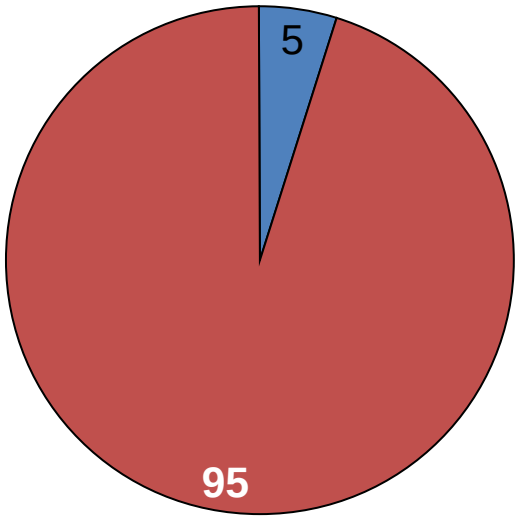
CDRH: Resource Concerns

FDA can only inspect a portion of firms

Percent of firms inspected
Domestic; Annual



Percent of firms inspected
Foreign; Annual

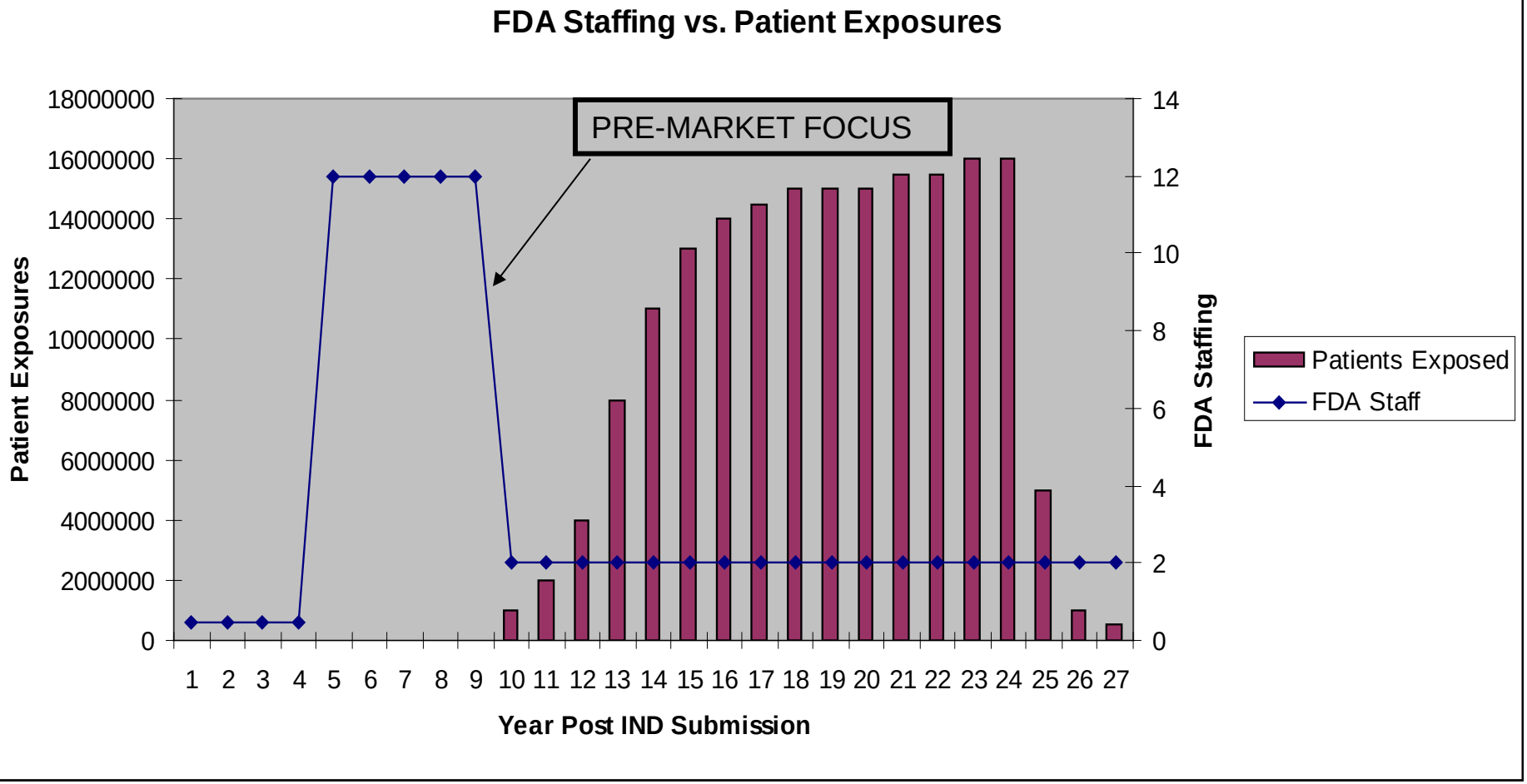


91 Warning Letters were issued in the 2011 fiscal year – 3% of total investigations[1] resulted in a Warning Letter

1 Counts both domestic and foreign investigations

* Presented by Steve Silverman at 2012 FDA/Xavier MedCon Conference

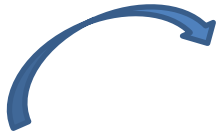
CDER: Historical Focus of Staff



*Presented by Russ Wesdyk at 2014 FDA/Xavier PharmaLink Conference

FDA Authority Differences

Drugs



CDER Call for Metrics

- FDASIA officially allows FDA to use risk based decisions to determine how best to use limited resources for drug inspections (Sec. 705)
- FDASIA allows FDA to request records in advance of or in lieu of an inspection (Sec. 706)
- FDA is not expressly given authority to use 3rd parties to assist with drug inspection coverage

Devices

CDRH Case for Quality

- FDASIA does not officially allow FDA to use risk based decisions to determine how best to use limited resources for device inspections
- FDA already had authority to use 3rd parties to assist with device inspection coverage

FDA Metrics Initiatives

CDRH: Case for Quality

- Launched in 2011 by Steve Silverman (former Director, CDRH Office of Compliance)

*
- FDA will continue to assess firms' compliance with the QSReg
- Both FDA and industry emphasize that good quality practices drive better products and protect public health
- FDA focuses with firms on root cause analysis, designing quality into the product, and optimizing corrective actions

* Presented by Silverman at FDA/Xavier MedCon Conference, May 2012

Case for Quality Key Goals:

1. Shift mentality from compliance to quality
2. Shift ownership of quality to firms, rather than reliance on, and reaction to, enforcement

- **May 2014:** Silverman asked Xavier to partner with CDRH to identify key measures for industry to use to assess risk to product quality
- **May 2015:** FDA/Xavier Initiative adopted by Medical Device Innovation Consortium, and converted top 3 measures to metrics (+ Pilot)
- **June 2016:** FDA/Xavier Final Recommendations (to be presented tomorrow!)

CDRH 2016-2017 Strategic Priorities

Promote a Culture of Quality and Organizational Excellence

GOAL: STRENGTHEN PRODUCT AND MANUFACTURING QUALITY WITHIN THE MEDICAL DEVICE ECOSYSTEM

- By September 30, 2016, develop metrics, successful industry practices, standards, and tools that manufacturers can use to evaluate product and manufacturing quality beyond compliance with regulatory requirements.
- By December 31, 2016, pilot voluntary use of product and manufacturing quality metrics and evaluation tools.
- By December 31, 2017, propose a voluntary program to recognize independent evaluation of product and manufacturing quality.

FDA Metrics Initiatives

CDER: Call for Metrics

Date	Description
2012	FDASIA Passed
2013	CDER Quality Metrics Initiative launched
2013 – 2015	Call for metrics from industry • ISPE, PDA, GPhA, PhRMA, BIO, etc. provided CDER with metrics ideas
2015 (July 28)	Draft Guidance: Request for Quality Metrics
2016 (June 24)	Draft Guidance: Quality Metrics Technical Conformance Guide

Xavier/PwC Initiative took a different approach

The Xavier Approach

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Identify Meaningful Metrics for Industry

To provide a system of metrics across the Total Product Lifecycle that:

1. Informs internal company decisions and triggers action
2. Shifts the Right-First-Time mentality closer to the initial days of development

Xavier Pharma and Device Approach

Divided into Teams by Phase of Production

Assessed Critical Systems

Identified Key Activities

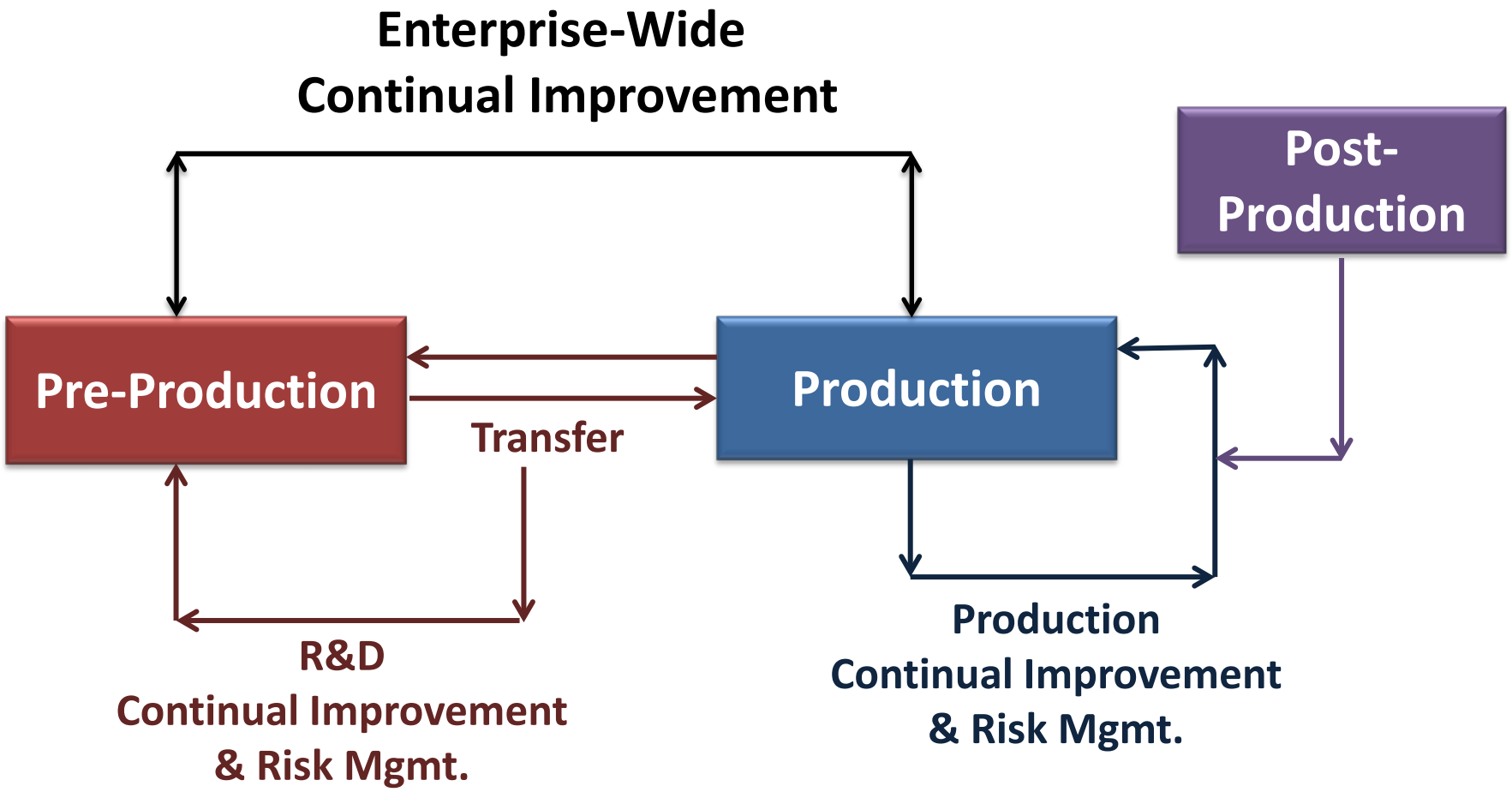
Determined How to Measure Activities

Assessed Using Cause and Effect Matrix Critical Criteria

Converted Measures into Metrics

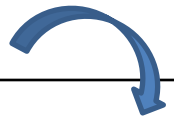
Not every idea is a good fit for the intended purpose

Teams by Phase of Production



Critical Systems

Device Systems	Pharma Systems
CAPA	Investigations
Change Control	Cont. Improvement & Change Mgmt.
Complaint Handling	Complaints/Deviations
Customer-Related/VOC	Registration & Notifications
Design Controls	Development Effectiveness
Distribution	Audits/Inspections
Management Controls	Management Engagement
Post-Launch Surveillance	Quality System Effectiveness
Production and Process Controls	Operational Excellence
Servicing	Quality Risk Management/Trending
Supplier Controls	



125 Measures Identified

97 Measures Identified

Cause & Effect Matrix

Critical Requirement >>>		Patient Safety	Supply Assurance	Quality System Robustness	Process Reliability	Failure Costs	
Importance Rating >>>		5	2	4	3	1	
	Measures List	**Degree of Correlation: Low --- 0, 3, 6, 9 --- High**					**Total**
1	Measure #1	9	6	3	0	3	**72**
2	Measure #2	0	9	9	3	0	**63**
3	Measure #3	3	0	0	0	0	**15**

- The critical requirements are weighted based on perceived importance
- Each measure is assessed for its correlation to the critical requirements
- The total score allows for a Pareto analysis to identify the measures that are most strongly correlated to the critical requirements

Metrics Comparison

TPLC Phases	FDA/Xavier Device Metrics	Xavier/PwC Pharma Metrics	CDER Draft Metrics
Pre-Production	Design Robustness	Design Space	
		Supply Chain Assurance	
Technology Transfer		RFT of Analytical Transfer	
		RFT of Process Validation	
Production	RFT for Production	RFT for Production	Lot Acceptance Rate
		CAPA Effectiveness Rate	
		Commitment Index	Invalidated OOS Rate
		Supplier Risk Index	
Post-Production	Post-Market Index	Market Reliability Index	Complaint Rate
Enterprise-wide	Management Review	QbD Effectiveness	APR on Time Rate
		Root Cause of RFT	

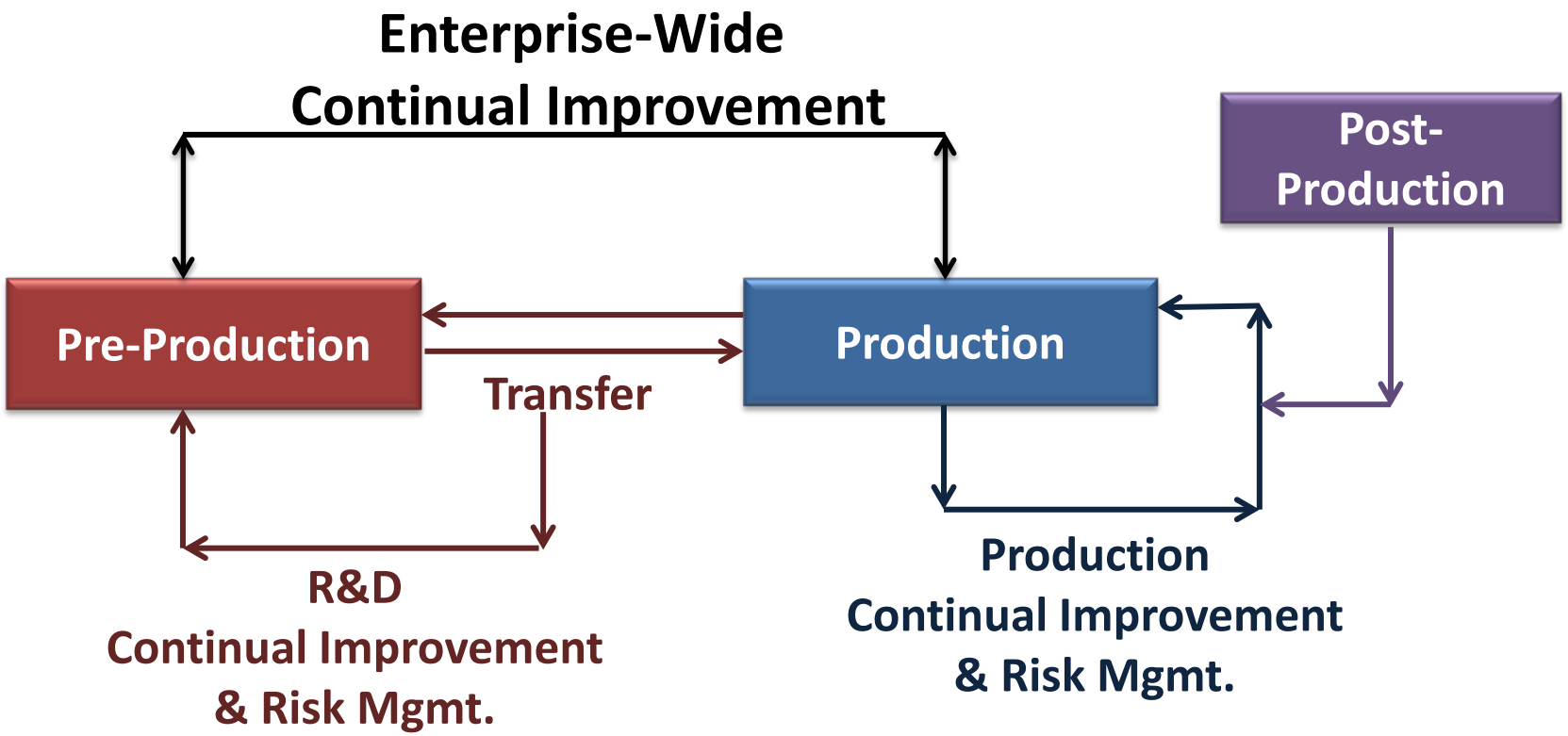
How to Use the Metrics?

The Metric is only a Number

- What is its relevance?
- How can it inform decisions and trigger action?
- How can you shift the Right-First-Time mentality closer to the initial days of development?

Pulling it all Together

- What is its relevance?
- How can it inform decisions and trigger action?
- How can you shift the Right-First-Time mentality closer to the initial days of development?



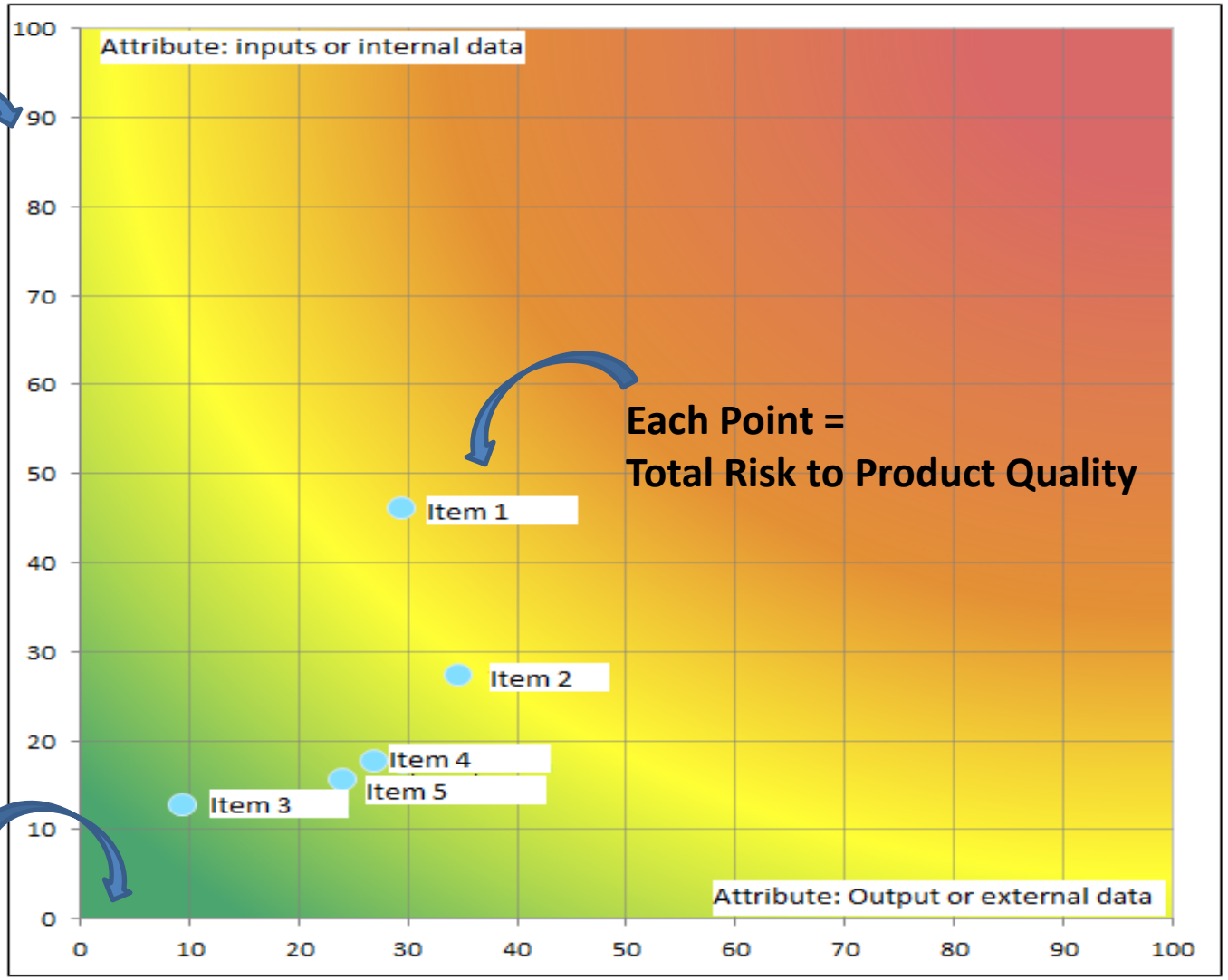
Heat Map Correlation

Y-axis =
Internal
Risk Score

"Internal" includes pre-production and production metric total risk score

X-axis =
External
Risk Score

"External" includes the total post-production risk score of appropriate indicators



Comparison of Metrics?

Comparison of Facility A versus Facility B

Challenges?

- Difference in definition of terms. What constitutes a non-conformance, etc.
- Risk Tolerance difference between senior management levels.
- Cultural differences - microcosm. Fear of recrimination at one facility versus another, even though same company.
- Gaming the numbers due to competition between sites.
- Difference in product complexity.

Comparison of Metrics?

Metrics Assessment	
Company A	**Company B**
1. RFT in Production = 91% • Decreased from 97% • Increased from 90% • Simple product and process 2. Complaint rate = 0.1 cpm • Pain medication • Rationalization and high risk tolerance	1. RFT in Production = 91% 2. Complaint rate = 0.1 cpm • Elderly population

How FDA Intends to Use Metrics

CDER and CDRH have both commented on the importance of assessing metrics in-context

- * Looking to identify risk-based factors that could impact inspection frequency
- * 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

* Presented by Tara Gooen at ISPE/FDA/PQRI Conference June 2016

ORA Perspective

Goals of New Inspection Protocol Project (NIPP)

To develop a new paradigm for inspections and reports that will advance pharmaceutical quality by:

- Providing a risk-based and rule-based process that uses expert questions
- Measuring and describing the state of quality in the inspected facility
- Using analyzable assessments (semi-quantitative scoring) that can track and improve performance.
- Enable comparisons between sites and over time for individual sites
- Recognizing and rewarding positive behaviors in cases where facilities exceed basic compliance

*Presented by Ellen Morrison at FDA/Xavier PharmaLink Conference, March 2016.

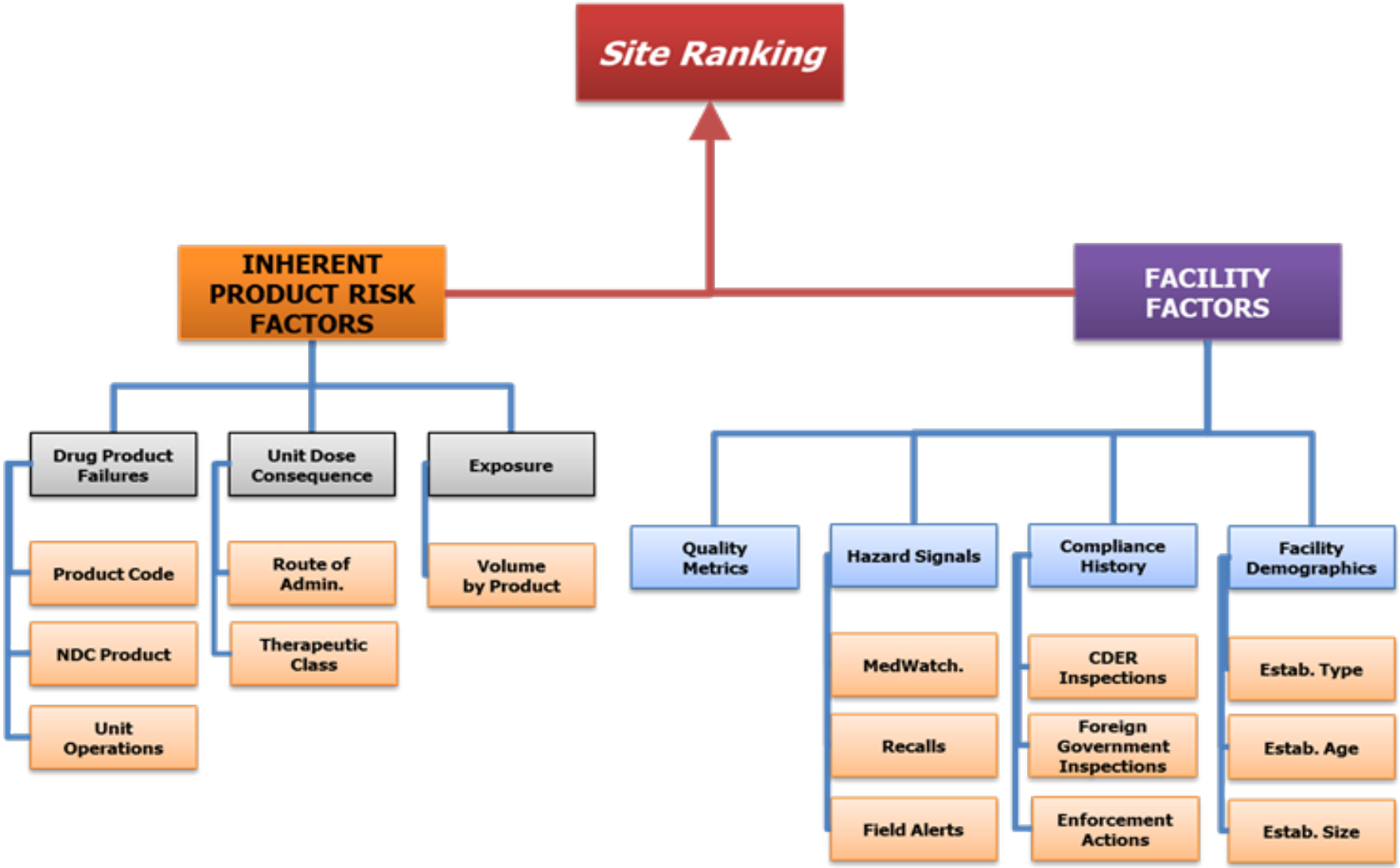
ORA Perspective

Collaborative Effort

(multiple relevant sources of info)

*Presented by Ellen Morrison at FDA/Xavier PharmaLink Conference, March 2016.

ORA Perspective



*Presented by Ellen Morrison at FDA/Xavier PharmaLink Conference, March 2016.

Xavier Asked Industry…..

What do you hope comes out of the CDER and CDRH metrics initiatives?

- Don't want inspections less frequently
  - Value the verification of practices
  - If less frequent, then impact of findings could be greater
- Want fewer inspections per year
  - Currently being inspected by multiple regulatory authorities in any given year
  - Mutual reliance efforts are key
- Want the playing field leveled with competitors (competitors need to be inspected also)
- Want one solution between CDER and CDRH since companies have both drugs and devices

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Questions…Ideas

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