Pinch-hitting @ The University of Heidelberg QbD / PAT Conference 2013

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Two talks you were expecting

- What to expect in the next 25 years of medicine?

Dr Janet Woodcock, Director CDER, FDA, USA

- The Role and Relationship of CGMP Statistics with Pharmaceutical Quality
  - Recent enforcement action examples
  - CGMP statistical references
  - Use of Consensus Standards for Pharmaceutical
  - Manufacturing quality

Dr Karthik Iyer FDA /CDER

"It is always a wild ride, but it's always interesting"

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FDA's Woodcock: What to expect in the next 25 years of medicine

October 23, 2011 | By Maureen Martino

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How has the biopharma industry evolved over the last 25 years, and what can we expect from the industry in the next two and a half decades? Those were questions CDER director Janet Woodcock set out to answer at the 25th annual AAPS meeting in Washington, D.C., on Sunday. In honor of the organization's 25th anniversary, Woodcock, who's been with the FDA since 1986, reflected on the industry's past and on trends she believes will play a major role in shaping biotech and pharma in the coming years.

The drug industry was very different when AAPS was founded in 1986, Woodcock said. The issue of the day was drug lag--that is, concern that new molecular entities were being approved and reaching patients in other parts of the world sooner than in the U.S. Many industry watchers believed the FDA review process was too slow to keep up with advances in medicine. From this era came the first Prescription Drug User Fee Act, which was instituted in 1992 and gave the agency funding necessary to process NDAs more quickly. A decade and a half later, the pendulum moved in the other direction. Those who had been clamoring for new drugs had become concerned that innovative medicines were not tested carefully enough, and drug safety became a major issue. Woodcock said the early 2000s presented a cautionary tale for the agency. "Society has rolling expectations," she warned.

The HIV epidemic emerged around the same time as the agency was wrestling with concerns about slow drug approval. "Suddenly there was an incredible sense of urgency all around to do something about this," Woodcock said. The industry, she said, did a great job rising to the challenge, while the FDA did its part with accelerated approval. As a result, HIV has gone from a death sentence to a

- Continuous manufacturing
- Molecular medicine
- Political turmoil
- Drug regulation will grow less intrusive and less complex
- EHRs will finally be standard

http://www.fiercepharma.com/story/fdas-woodcock-what-expect-next-25-years-medicine/2011-10-23

“…I am not planning to retire as erroneously reported…”

FierceBiotech

FDA's Woodcock: I'm not going anywhere

"I want to assure you that I am not planning to retire as erroneously reported in the media today," she said. "In fact, quite the opposite is true. I am becoming more deeply involved in many of the Center’s issues, including the proposed reorganizations of the Office of Pharmaceutical Quality (OPQ) and the Office of Generic Drugs (OGD)."

Shifting the way FDA operates….

Vision 2020- I can see clearly now

- Quality & performance by design + Continuous "real time" monitoring of quality
- Specifications based on mechanistic understanding of how formulation and process factors impact product performance
- High efficiency and capacity utilization
- "Real time" review and inspection from Rockville, White Oak, NJDO,…

Globalization requires fundamental shift in the way FDA operates

- Establishment of foreign offices
- Increased foreign inspections
- Risk-based monitoring and inspections
- Global collaborations to harmonize standards and leverage resources
- Investing to strengthen regulatory systems abroad
- Efforts to combat counterfeit and substandard drugs
- Implementation of legislative mandates (FDASIA)

A decade ago

THE WALL STREET JOURNAL.

Factory Shift

New Prescription For Drug Makers: Update the Plants

After Years of Neglect, Industry Focuses on Manufacturing; FDA Acts as a Catalyst

The Three-Story Blender

By Leila Abboud And Scott Hensley

3 September 2003

Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach

Final Report - Fall 2004

Department of Health and Human Services, U.S. Food and Drug Administration

September 2004

This Report is also available in PDF (214KB)

Comments & challenges

Comments

- "Generics are all about file first and figure out later"
- "R&D is incentivized on shots on goal not QbD"
- "We really don't understand what effects what"
- "Huge amount of reviewer inconsistency"

Challenges

(fully implemented)

- Alignment with 3rd parties
- Regulators not prepared
- Current interaction (FDA) not conducive to QbD

Data from: Ted Fuhr, McKinsey & Company. 17 July 2011: FDA Advisory Committee Presentation

CGMP Statistics and Pharmaceutical Quality

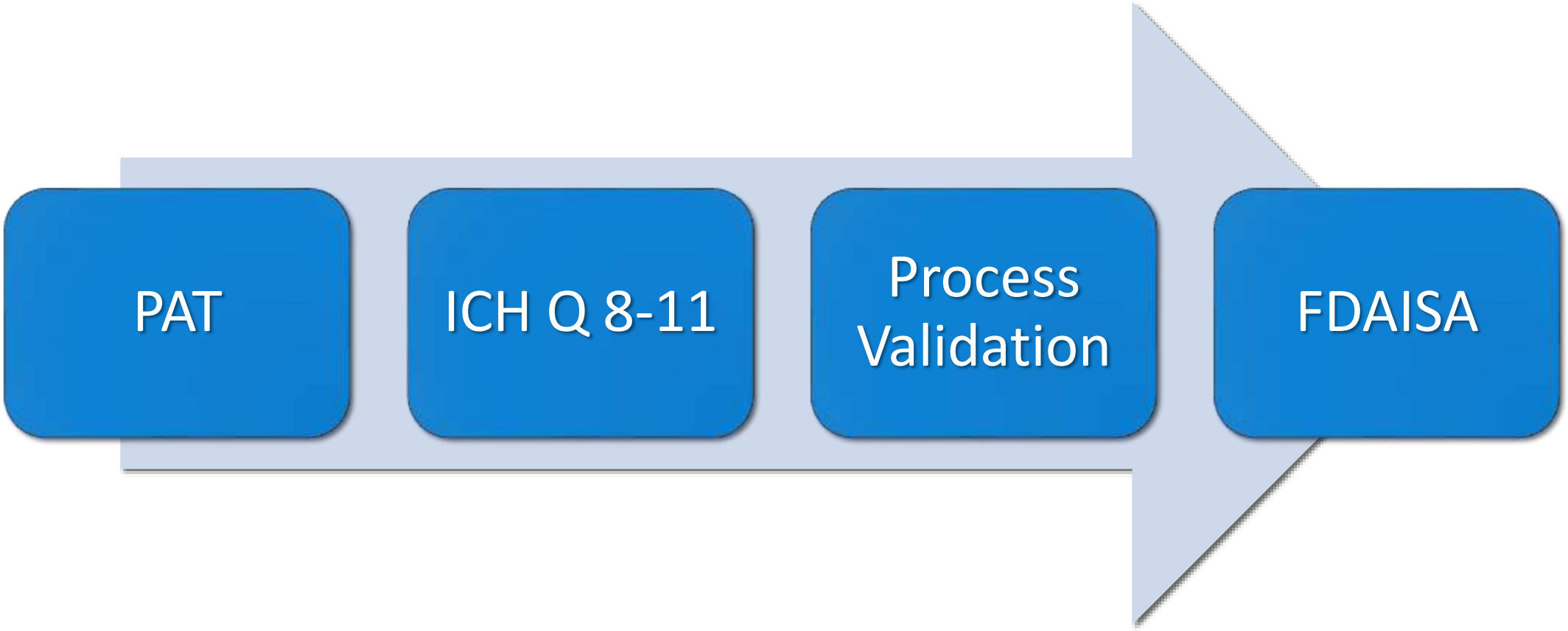
Process validation

- Stage 1: Process Design
- Stage 2: Process Qualification
- Stage 3: Continued Process Verification

ASTM

- ASTM E2474-06 Standard Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology.
- ASTM E2476-09 Standard Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture.
- ASTM E2281-03 Standard Practice for Process and Measurement Capability Indices.
- ASTM E2500-07 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment.
- ASTM E2709-10 Standard Practice for Demonstrating Capability to Comply with a Lot Acceptance Procedure.

Risk-based monitoring & inspections



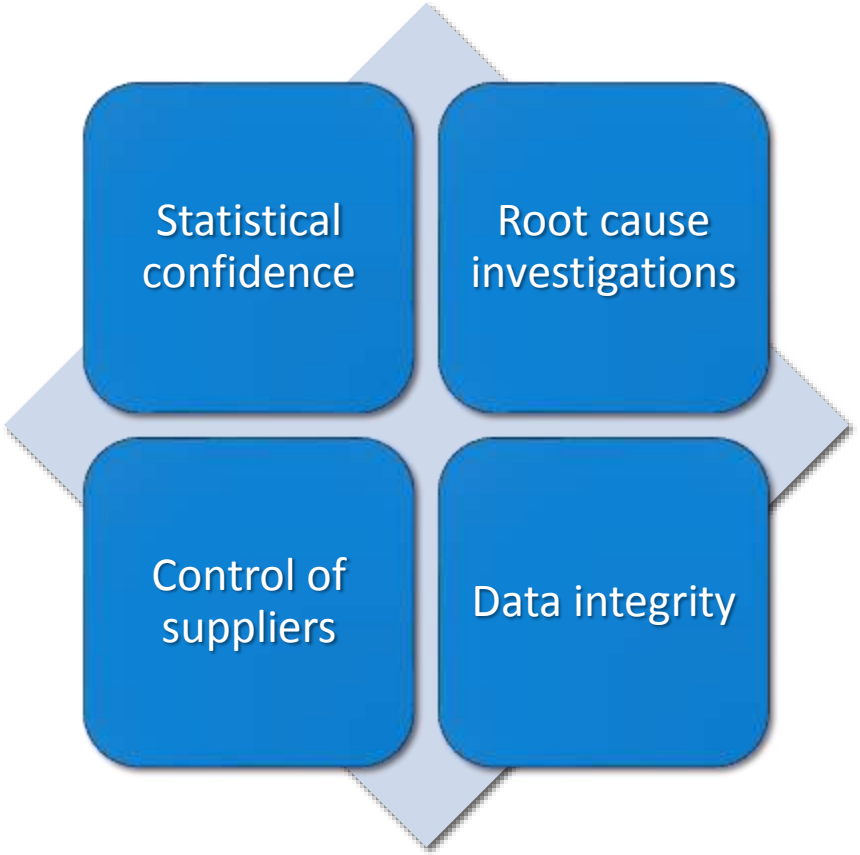
FDA expects more statistical thinking in validation

A high percent of the population is within specification

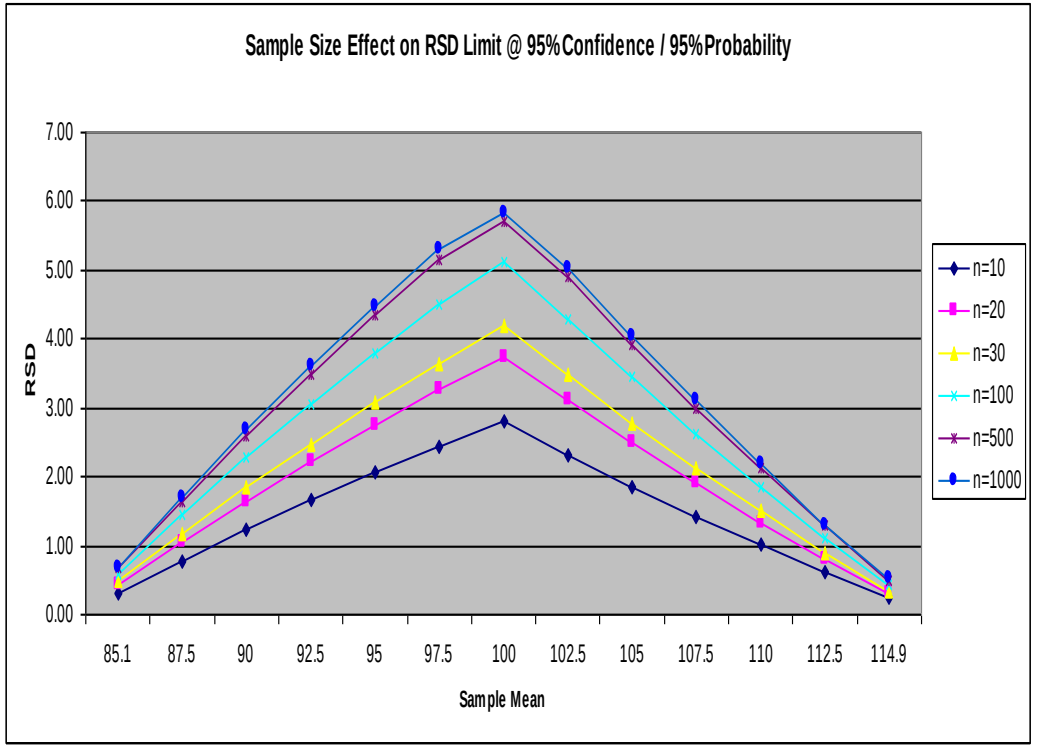
A population parameter is within specification
- Mean; Standard Deviation; RSD; Cpk/Ppk

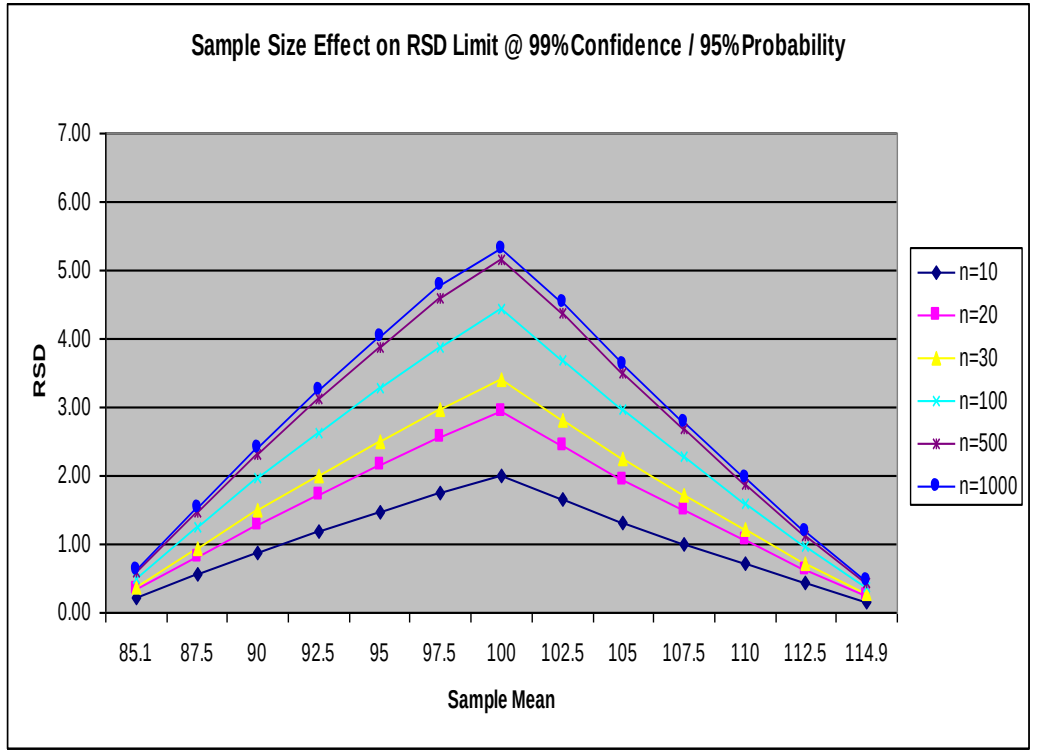
A standard test (UDU, Dissolution, etc.) will pass

Enforcement actions



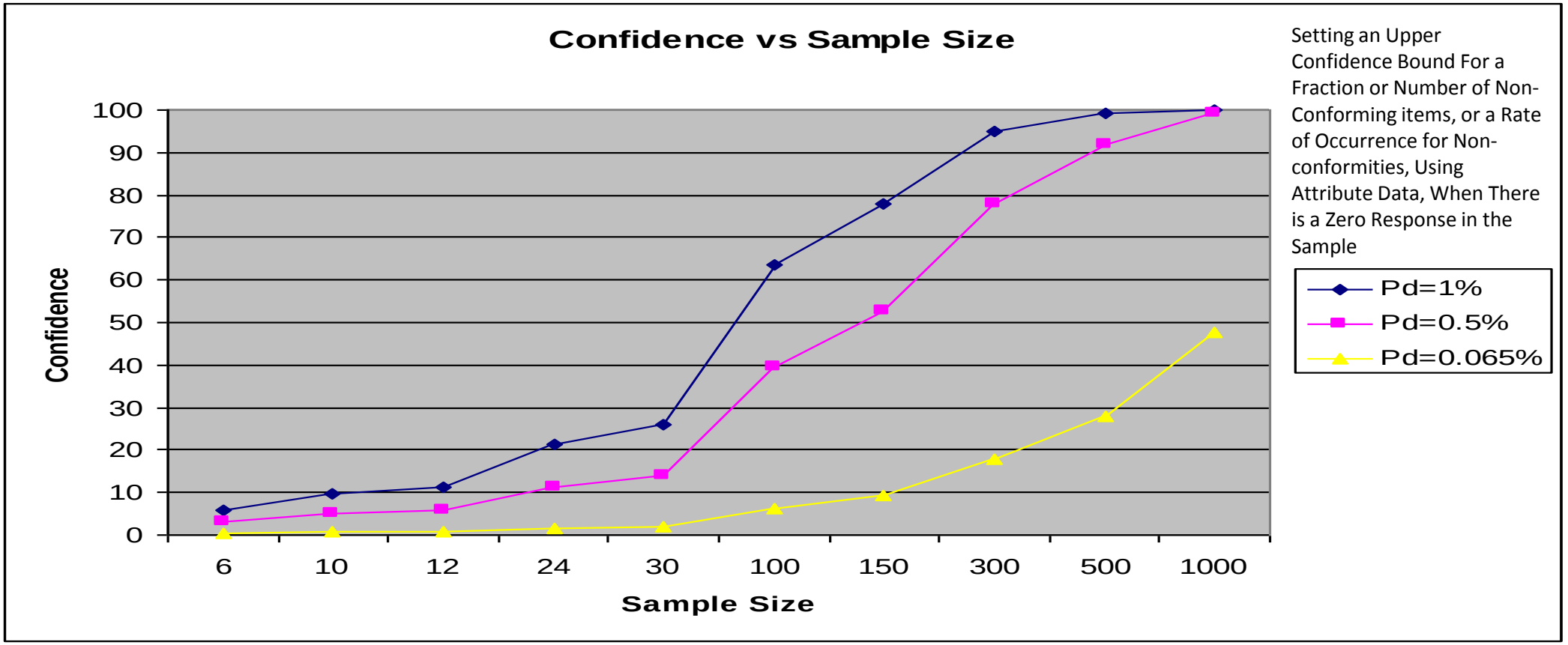
ASTM E2709 Standard Practice for Demonstrating Capability to Comply with an Acceptance Procedure





Karthik Iyer

ASTM E2334:



Karthik Iyer

Sampling plan, capability, stability

Capability

- Can the system consistently make product that meets specifications?
- The demonstrated CPK ensures that Critical Quality Attributes (CQAs) are consistently met
- The CPK meets requirements of other steps in the process, particularly for in process data

Stability

- Can the system consistently make product that meets specifications?
- Does the system ensure consistent product, even with varying inputs?
- Common cause variation or special cause variation?

Common Investigation-Related Findings

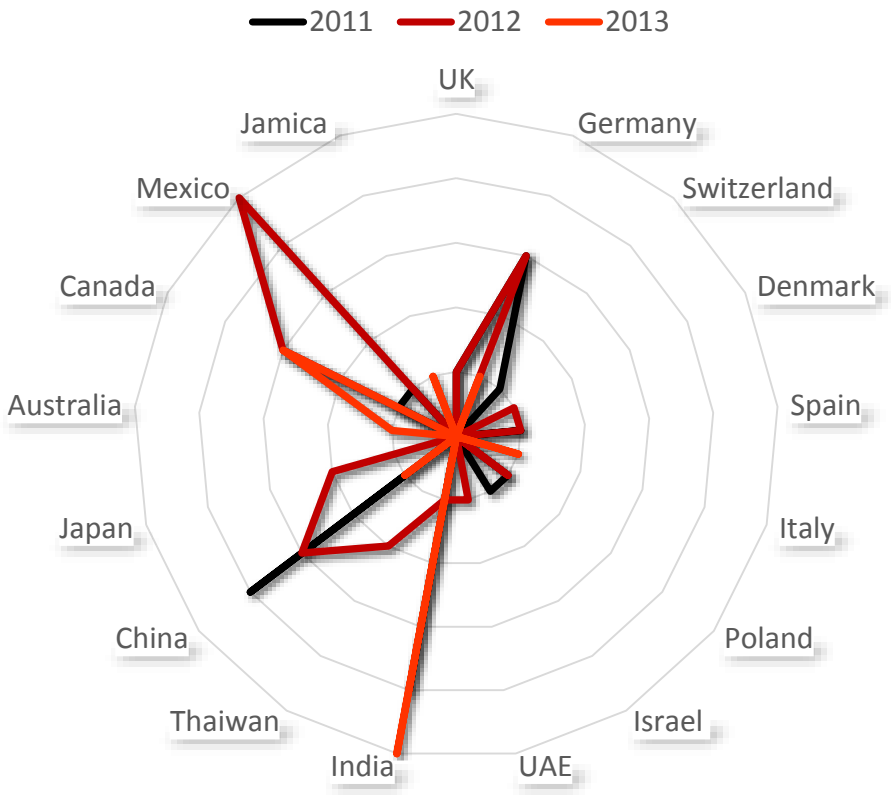
- Failure/OOS SOPs usually good, but not followed
- OOS's are tested into compliance
- Complaints not substantively investigated
- Adverse complaint trend not detected or investigated
- Scope of Investigations (see 211.192): *isolated issue or recurring?*
- Appropriate expertise (SMEs) to investigate/diagnose/correct

Rick Friedman

Every batch, Every day…

We rely upon the manufacturing controls and standards to ensure that time and time again, lot after lot, year after year the same clinical profile will be delivered because the product will be the same in its quality…" Janet Woodcock

FDA CDER Warning Letters 2011-2013 (August)



Selected media clips

http://www.raps.org/focus-online/news/news-article-view/article/3837.aspx http://www.ipqpubs.com/news/

Reasons for concern

Egregious violations noted and increasing frequency and rigor of inspections

Decreased *risk tolerance* going forward

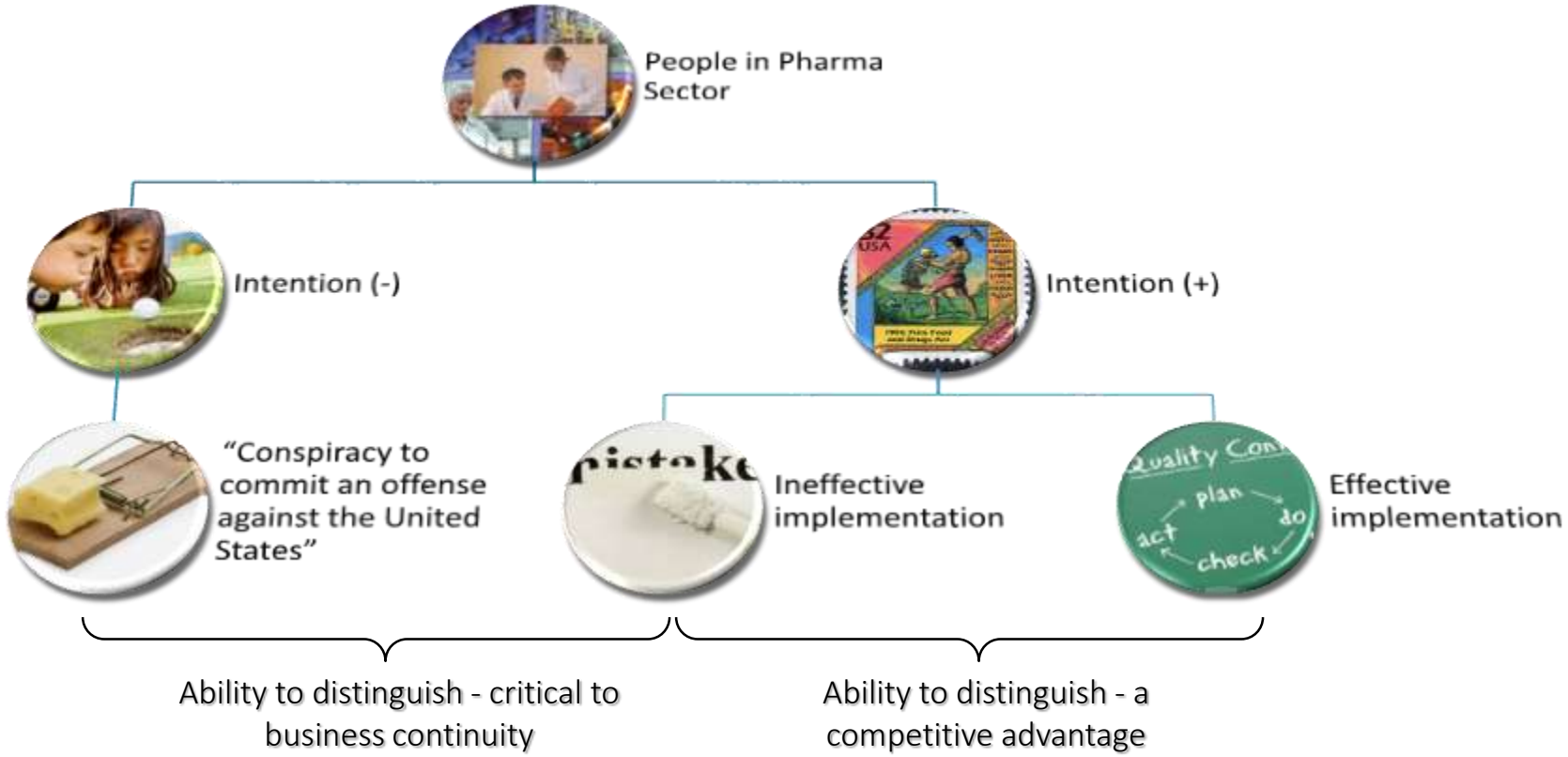
Gaps in understanding and in effective communication

Many changes in the *US regulatory and legal landscape*

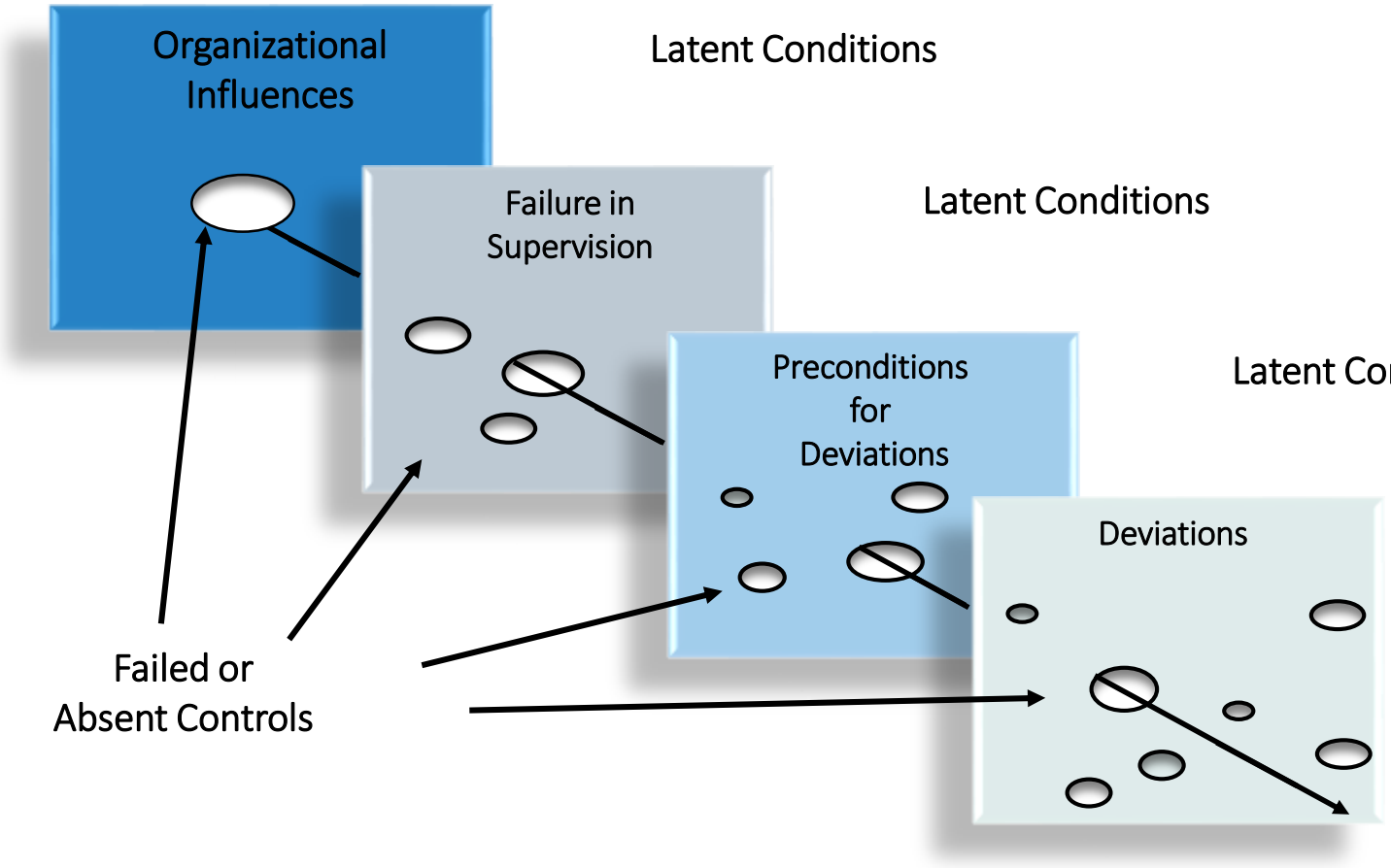
Behaviors - outcome based; how you get there not aligned with subtleties of GXP

Key challenges are *people issues*; solutions need to be across the enterprise

Distinguishing between cognitive biases & cheating by design



Human Factors Analysis and Classification System for CGMPs



Reason, J. *Human Error,* New York, and Cambridge: Cambridge University Press, 1990

Shappell, S. A. and Wiegmann, D. A. "The Human Factors Analysis and Classification System -- HFACS." Washington: US Department of Transportation, Federal Aviation Administration, Office of Aviation Medicine, 2000.

Steps to improve patient protection in the US*

Decreased risk tolerance

- In US serious quality issues noted in both imported and domestic supplies
- Control of imports more difficult; higher concern
- Detections and resolution not optimal
- Confidence reduced in the System

US regulatory landscape

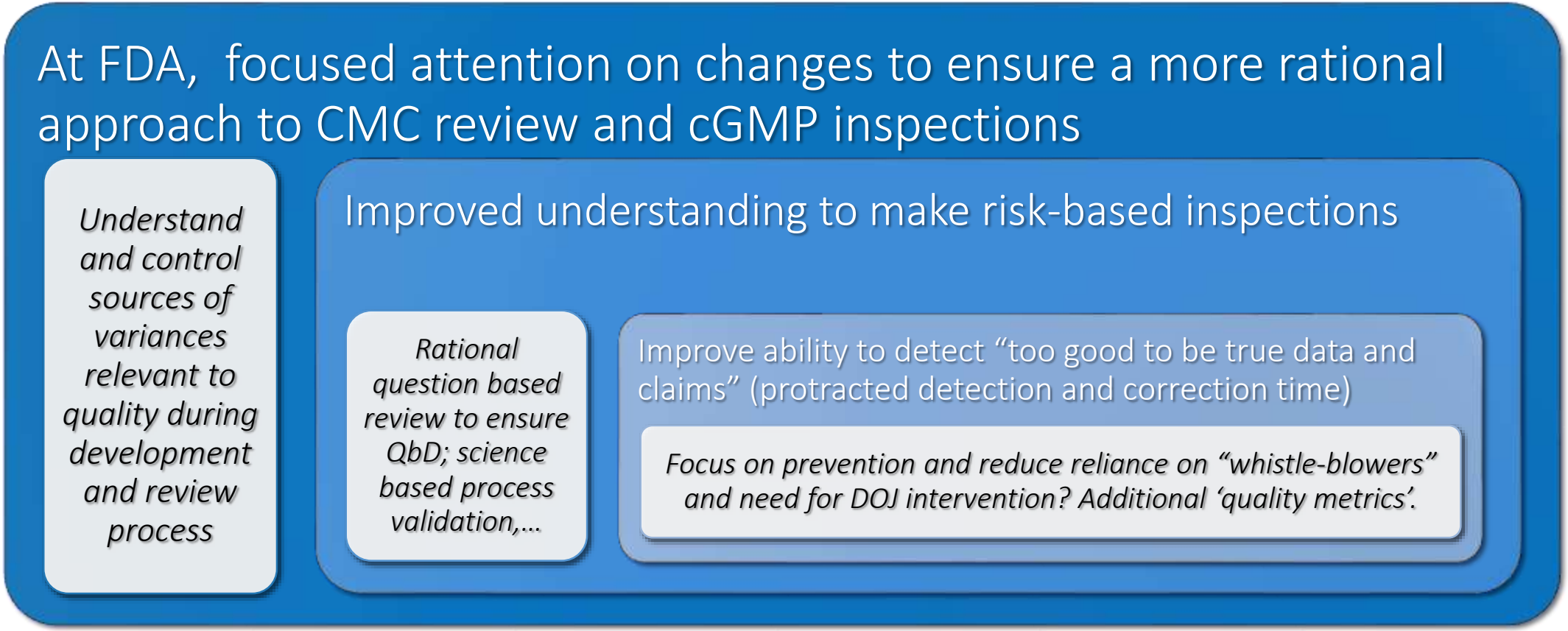
- FDA authority increased under FDASIA
  - cGMP definition expanded
  - User fees
  - Review changes
  - Types and capacity of inspections increased
  - FDA India
- cGMP violations & False Claims Act

People issues

- Counterfeits, adulteration
- Adulteration in the US points to *intention* इरादा (document what you do and do what you document)
- Current system heavy on SOP's –easy to say 'Great Mounds of Paper'
- With FDA's encouragement a new paradigm in manufacturing is visible

*Similar efforts globally; although not discussed in the presentation these are considered

Changes at FDA CDER……



Consider the following

2014 – : FDA's ability to detect will increase rapidly

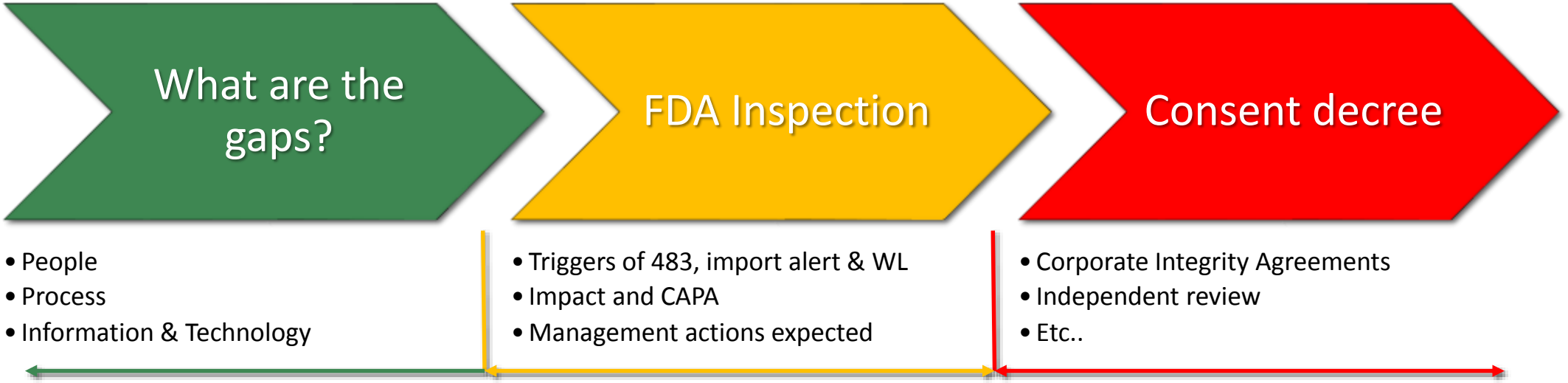
- "FDA's goals in India .. better and more robust information to help FDA officials in the various FDA headquarter Offices… at the borders make better decisions about the products from India ..developed for the U.S. market." (FDA website)
  - Focused and frequent inspections
  - Whistleblowers encouraged
  - Manufacturing metrics? "too good to be true"
  - Rigorous question based review and alignment between review and compliance functions

By 2020: Market-manufacturing dynamics to shift significantly

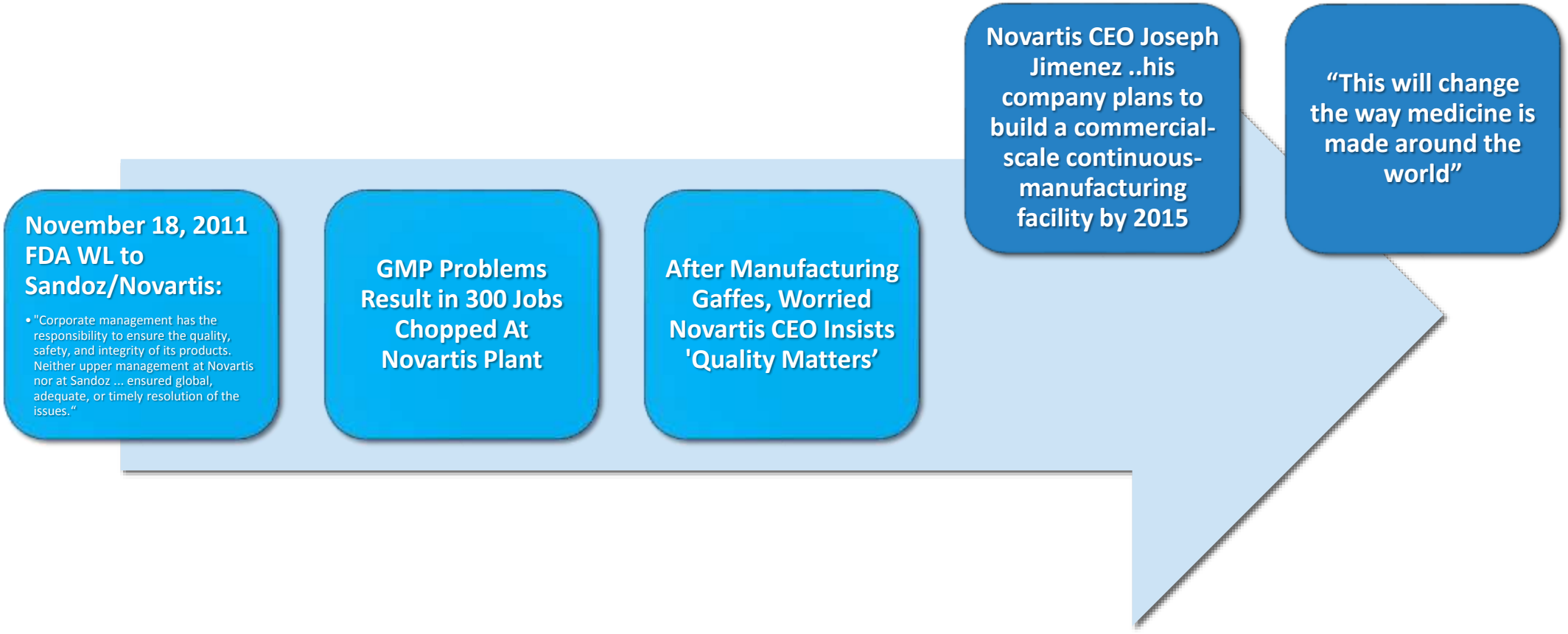
- Novartis CEO Joseph Jimenez -company plans to build a commercial-scale continuous-manufacturing facility by 2015 (MIT Technology Review November 6, 2012)
  - UK pushes continuous manufacturing (March 24, 2011)
  - PAT, QbD spur continuous processing (April 5, 2011)
  - Sanofi's Genzyme looking hard at continuous manufacturing (January 31, 2013)
  - GSK commits to continuous processing (February 19, 2013)

FiercePharma Manufacturing

Prevention: Why, How & What?



Are we at a tipping point?



http://www.technologyreview.com/view/427895/the-future-of-pharma-is-incredibly-fast/

Are we at a tipping point?

Eli Lilly	• plans to have installed and demonstrated four separate continuous processing platforms by early next year.
GSK	• "We've started to deploy the first production versions in UK factories," Witty told investors. • Invest $50 million to install and validate commercial-scale continuous processing equipment at a plant in Singapore
Pfizer	• Already evolved towards a hybrid model between continuous and batch processing, with continuous approaches in areas such as coating and crystallization sitting alongside traditional batch systems
The PROMIS Centre	• officially launched on 19 February 2013 to provide R&D on the use of continuous processing of solid dosage form pharmaceuticals

http://www.pharmafile.com/news/181079/pharma-makes-progress-continuous-processing

GXP Puzzle to Performance

Guiding principles

1. Protect patients
2. Protect shareholder value
3. Competitive advantage

Self- detection, correction, prevention and improvement is required, expected and encouraged

- What if we find something objectionable?
  - A common concern
  - Correction and prevention the best option
- Structured program
  - Regulatory strategies for improvement, inspection, and submission
  - Confidence in data for sound decision making
  - Risk-based impact assessments and specific steps to strengthen GXP systems and improved process understanding and controls
  - Improving product development to address evolving requremtns of QbD
  - People development through training and mentoring
  - Corporate Voice for Quality - optimal management oversight via effective business process analytics and controls pertaining to quality of products (pharmaceutical and documents)

What will be your strategic response?

Detect, Correct, Prevent and/or Improve

- Customer focused
- Positive environment
- Competitive advantage

Remediation after an FDA 483, Import Alert or WL

- Customer focus questionable
- Negative environment
- Loss of shareholder value