MEDASSURE

SECURING YOUR SUPPLY CHAIN

Securing the Supply Chain: Combating evolving risks in drug sourcing & manufacturing

Dinesh S. Thakur
Executive Chairman

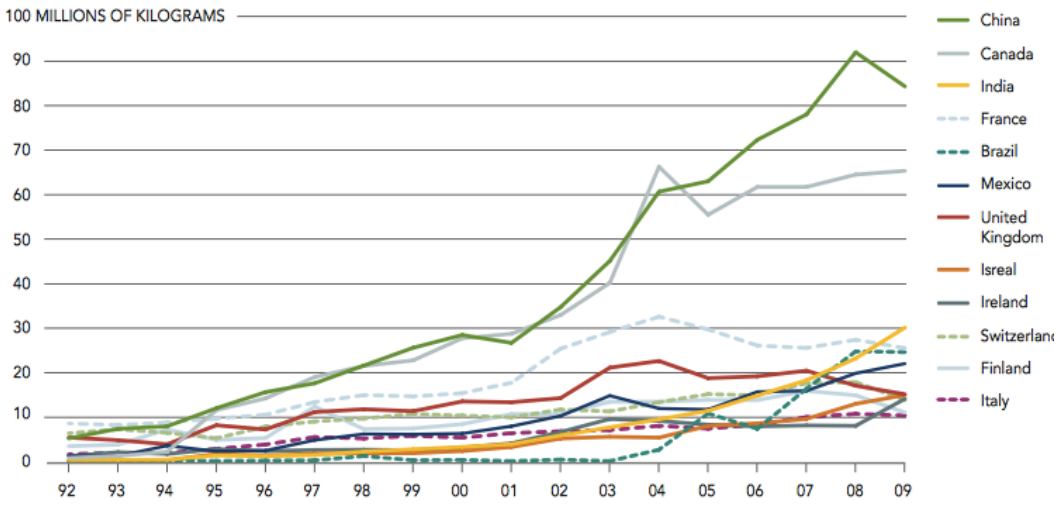
Agenda for today's presentation

- Set the context: How important is the Chinese pharma industry to the US market?
- What lessons can we learn from what has happened to the Indian pharma industry?
- What can the industry in China do to avoid a situation like India?
- How is the US FDA looking at product quality?
  - What does it mean for the industry?
- Q&A

Setting the context: Importance of China to the US

Figure 8

Top 12 source countries for U.S. imports of pharmaceuticals and medicines by weight (kg) from 1992 to 2009



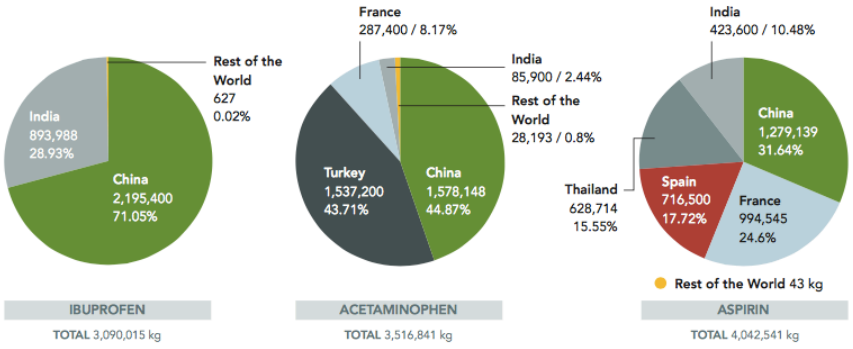
(Ranking based on 2009 data.)

Source: U.S. Census Bureau, Foreign Trade Division.[127]

Source: The Pew Charitable Trusts

Figure 9

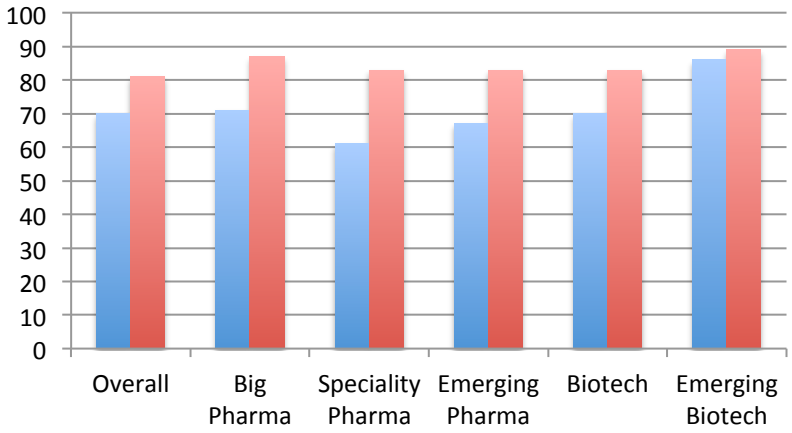
Top source countries for U.S. imports of ibuprofen, acetaminophen and aspirin by weight (kg)in 2009



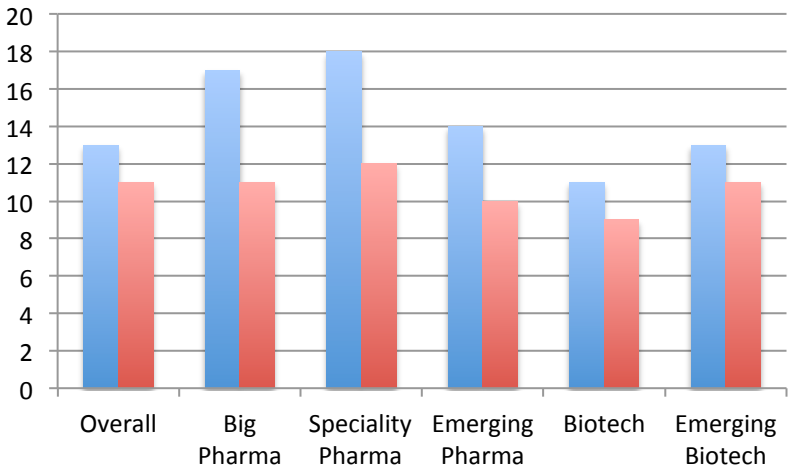
Source: U.S. Census Bureau, Foreign Trade Division.[128]

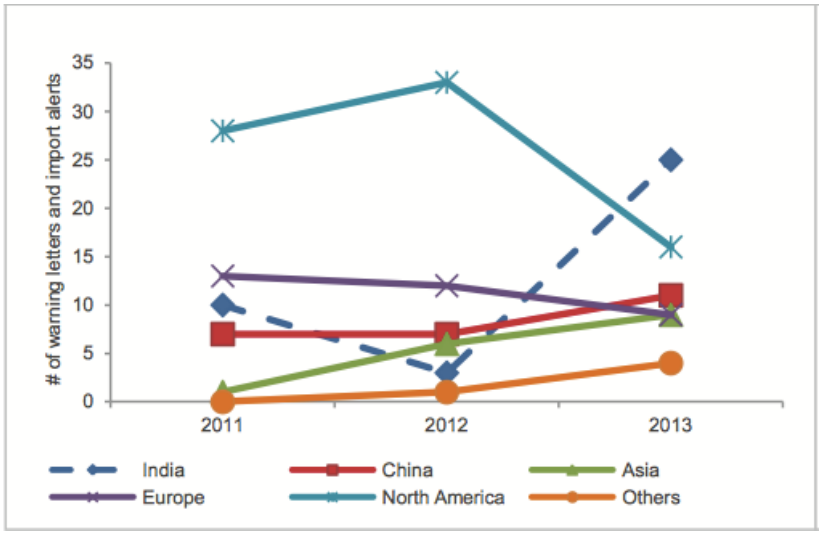
Trends affecting the pharma industry in India

Percentage of Respondents who would consider outsourcing to CROs/CMOs in Emerging Markets



Percentage of Outsourced Projects assigned to India

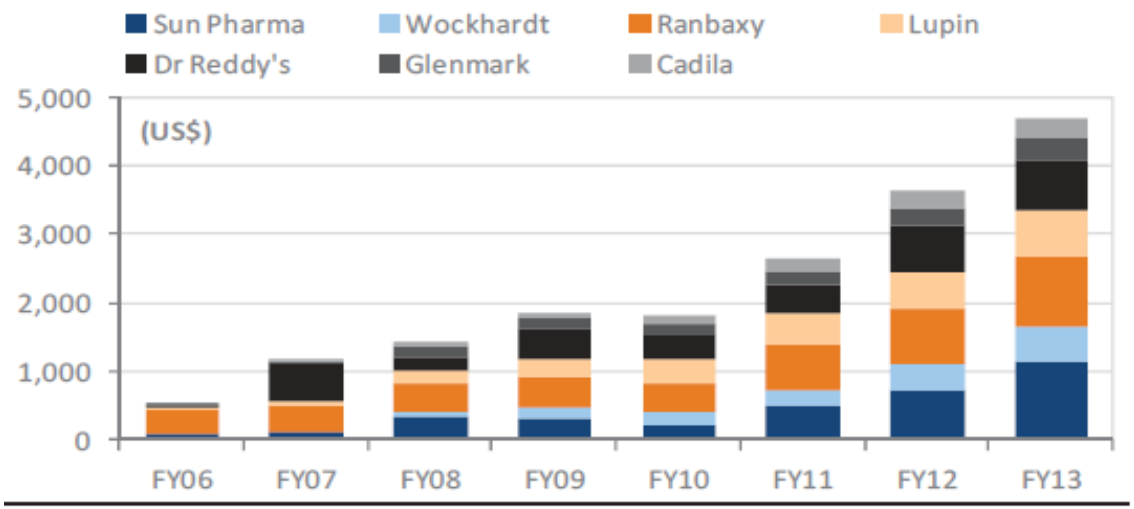




Source: What does 2015 hold for Indian industry? TJ Ladage, Life Sciences Leader, February 25, 2015

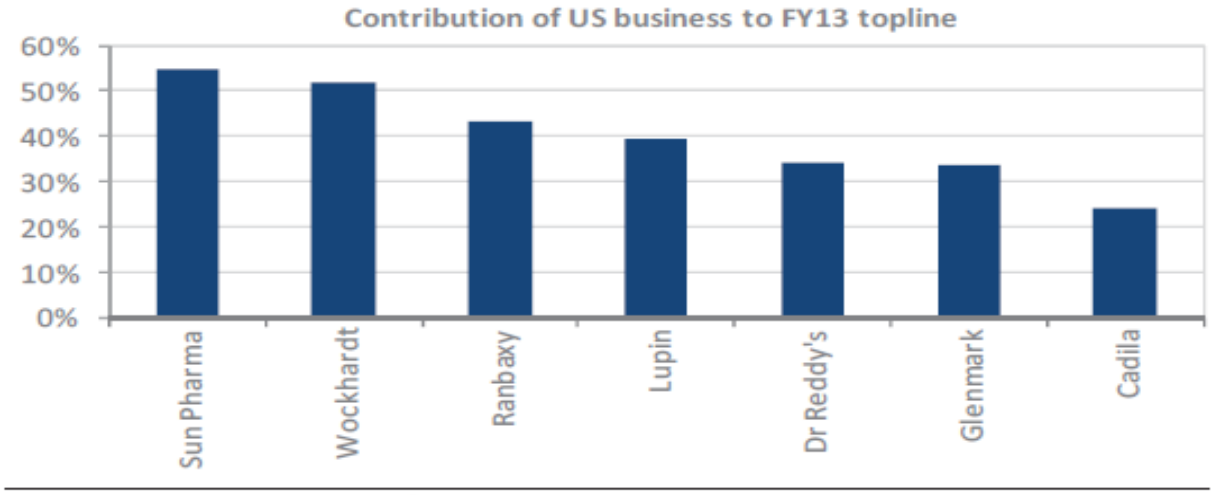
Importance of the US market to Indian companies

Figure 5: Indian players' US revenue grew from $600 to $4.5b in seven years



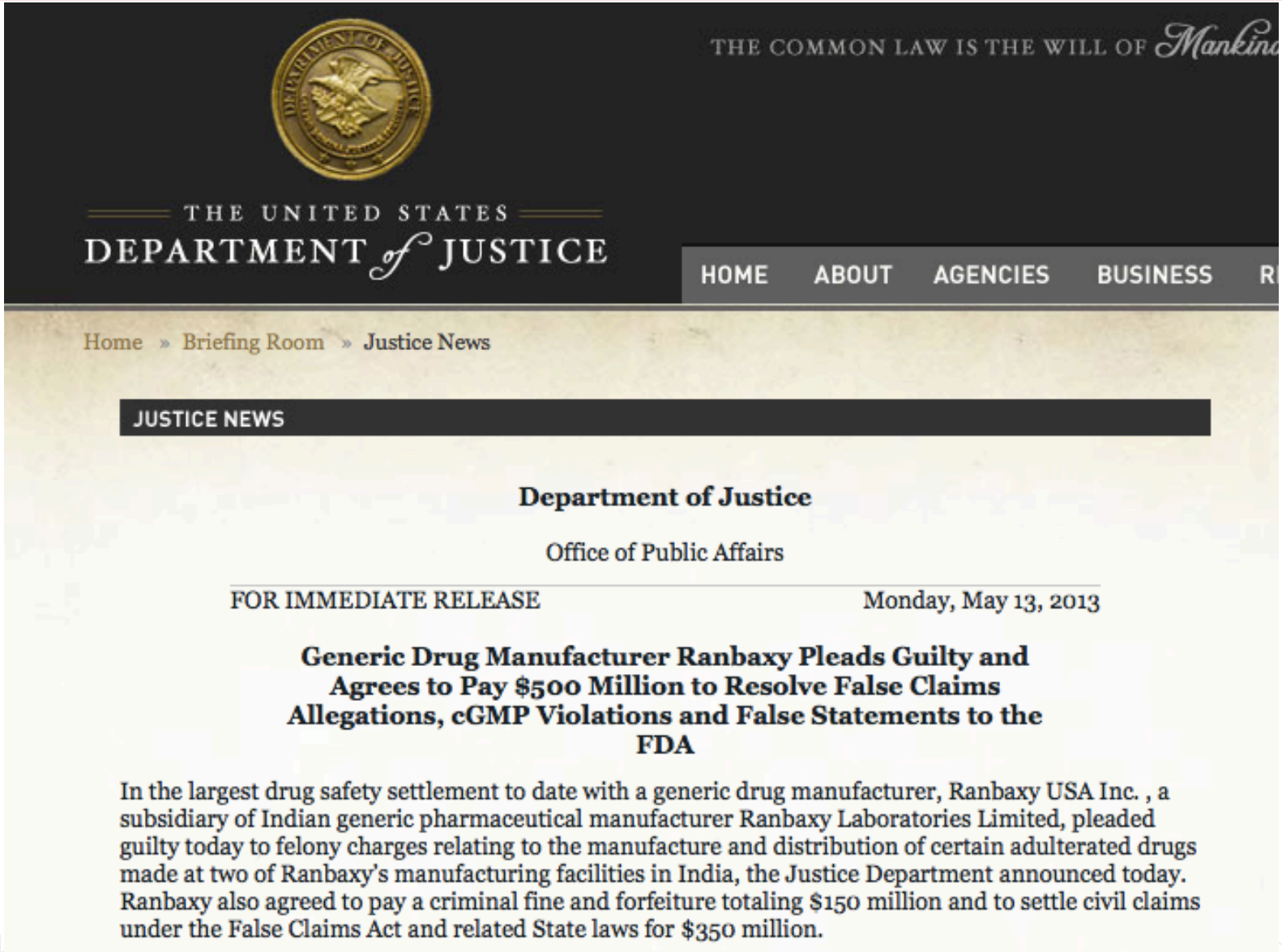
Source: Companies, IIFL Research

Figure 1: The US has become the largest business by far for large Indian pharma



Source: Companies, IIFL Research

My Story



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JUSTICE NEWS

Department of Justice

Office of Public Affairs

FOR IMMEDIATE RELEASE Monday, May 13, 2013

Generic Drug Manufacturer Ranbaxy Pleads Guilty and Agrees to Pay $500 Million to Resolve False Claims Allegations, cGMP Violations and False Statements to the FDA

In the largest drug safety settlement to date with a generic drug manufacturer, Ranbaxy USA Inc. , a subsidiary of Indian generic pharmaceutical manufacturer Ranbaxy Laboratories Limited, pleaded guilty today to felony charges relating to the manufacture and distribution of certain adulterated drugs made at two of Ranbaxy's manufacturing facilities in India, the Justice Department announced today. Ranbaxy also agreed to pay a criminal fine and forfeiture totaling $150 million and to settle civil claims under the False Claims Act and related State laws for $350 million.

The Outcome of my case

Case 1:13-cr-00238-JFM Document 7 Filed 05/13/13 Page 1 of 10

U.S. Department of Justice

United States Attorney
District of Maryland
Southern Division

Civil Division
Consumer Protection Branch

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MAY 13 2013

AT BALTIMORE
CLERK U.S. DISTRICT COURT
DISTRICT OF MARYLAND
BY DEPUTY

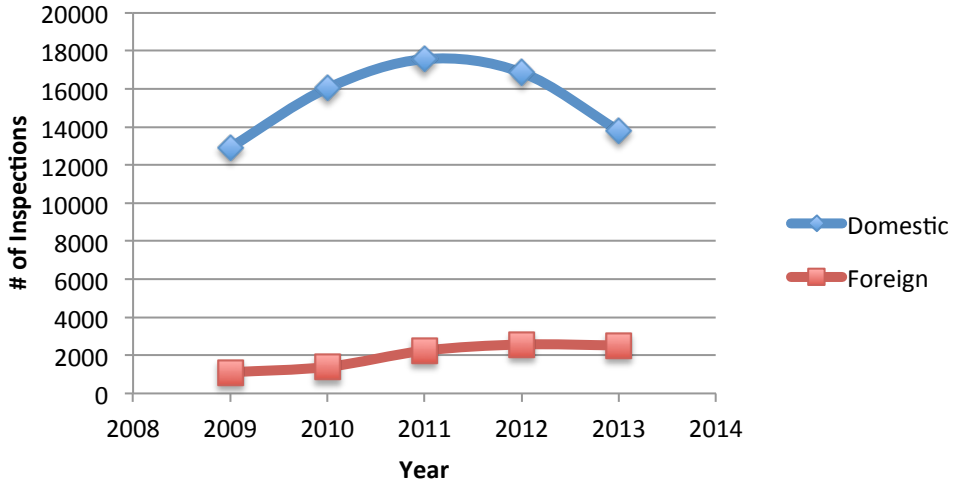
Offenses of Conviction

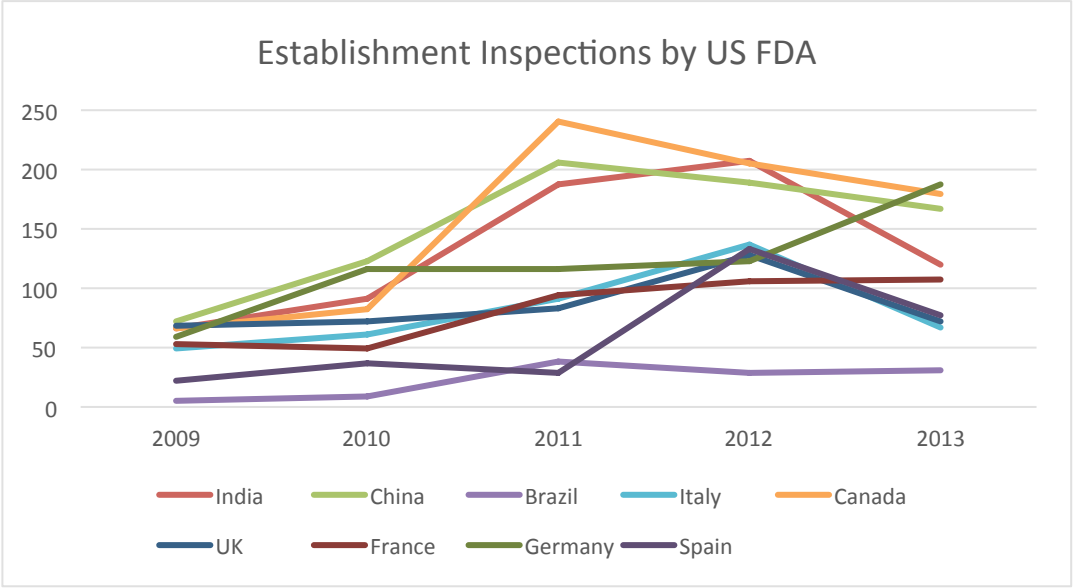
1. The Defendant agrees to knowingly and voluntarily waive indictment and plead guilty to Counts One through Seven of a criminal information to be filed against it, which will charge it with introduction into interstate commerce of adulterated drugs, with intent to defraud or mislead, in violation of 21 U.S.C. §§ 331(a), 333(a)(2), and 351(a)(2)(B); failure to timely file required reports with intent to defraud or mislead, in violation of 21 U.S.C. §§ 331(e) and 333(a)(2);

What Ranbaxy pleaded to

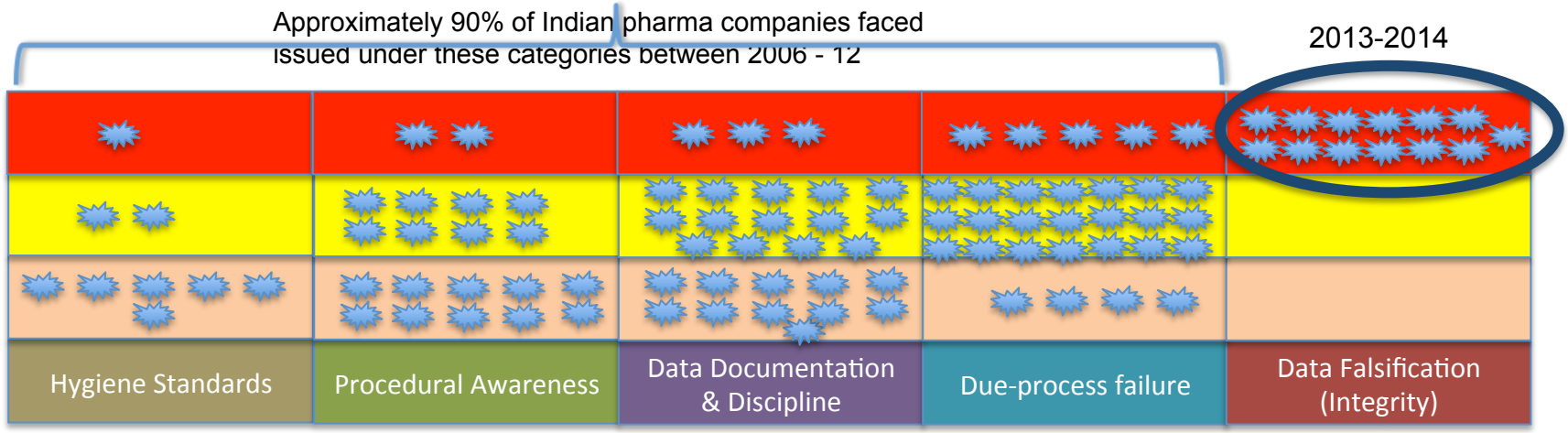
Ranbaxy knowingly manufactured, distributed, and sold in interstate commerce, and made false statements (including in annual reports to the Food and Drug Administration) about, certain batches, lots, or portions of lots of the Covered Drugs during the period referenced above in violation of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 331, 351, 352, and 355, including batches, lots, or portions of lots of the Covered Drugs (1) the strength of which materially differed from, or the purity or quality of which materially fell below, the strength, purity, or quality which they purported or were represented to possess, or (2) that were not manufactured according to the approved formulation and were, therefore, unapproved new drugs, in violation of the FDCA, 21 U.S.C. §§ 331(d) and 355(a), and were not "covered outpatient drugs" under 42 U.S.C. § 1396r-8(k)(2).

Impact of FDAsia





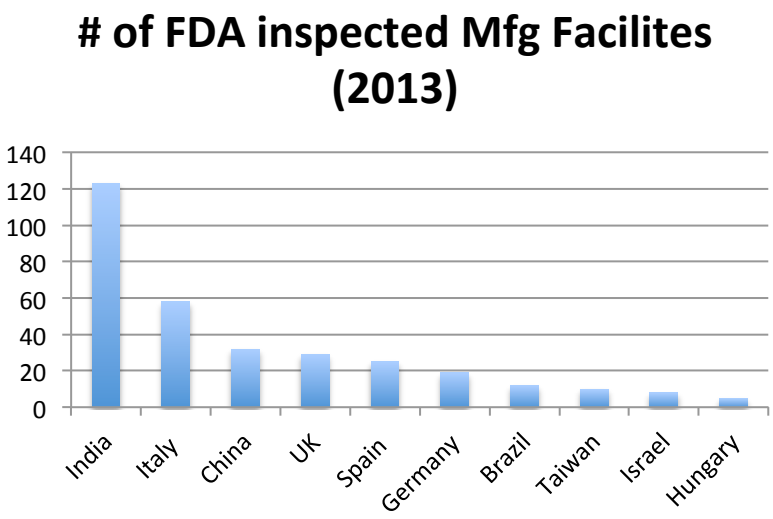
India has a systemic problem

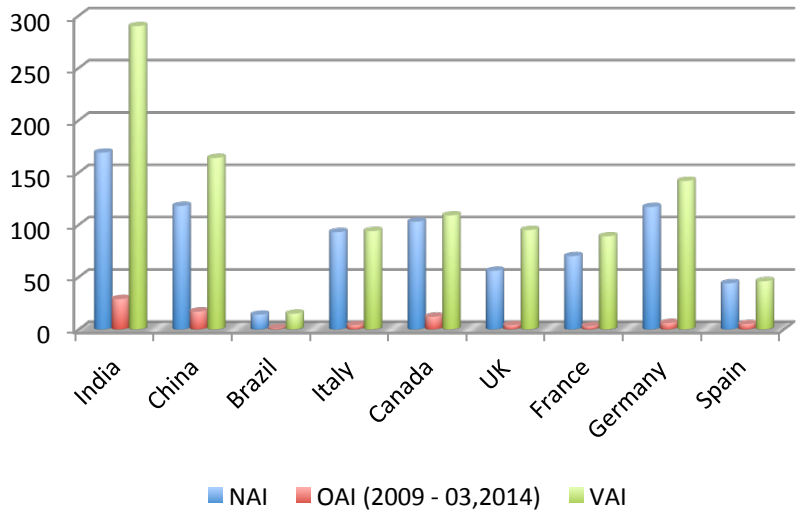


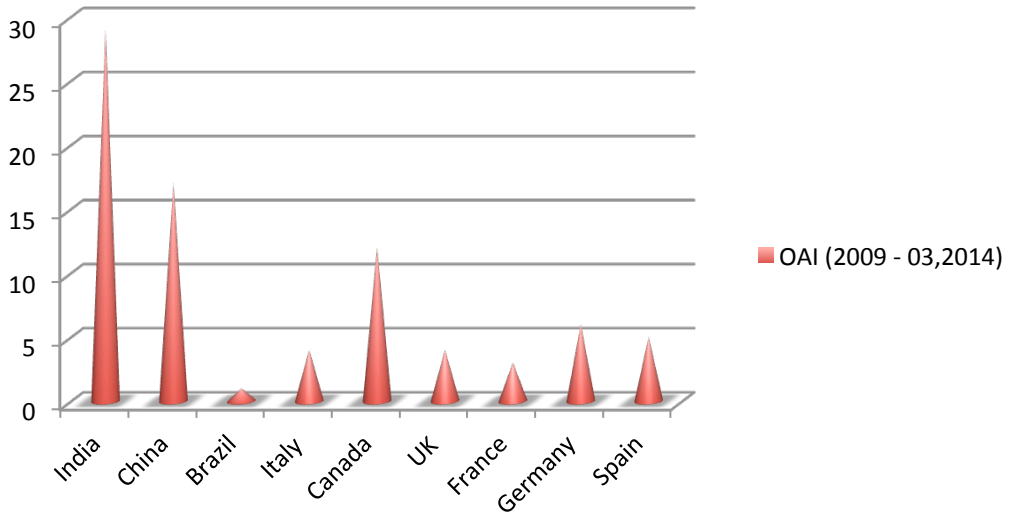
	Hygiene Standards	Procedural Awareness	Data Documentation & Discipline	Due-process failure	Data Falsification (Integrity)
Examples:	Failed to establish appropriate written procedures designed to prevent microbial contamination Failed to maintain buildings in a clean and sanitary condition Failed to provide adequate washing and toilet facilities to employees	Failed to ensure that each person engaged in the manufacturing and handling of the drug product has necessary education, training and experience	Laboratory records did not include complete data derived from all tests necessary to assure compliance with established specifications & standards	Failed to thoroughly investigate any unexplained discrepancy of a batch to meet any of its specifications Failed to follow required laboratory control mechanisms and to records and justify any deviations Failed to protect computerized data from unauthorized access or changes	Testing into compliance Creating false ECGs Repeatedly delayed, denied, limited an inspection or refused to permit the regulatory inspection Data inconsistencies: Person reported as supervisor for the operation not present on the dates the operation was conducted

Data represents enforcement actions faced by Indian pharmaceutical companies
Source: CRISIL

Compliance with cGMP is a key priority for the US







Physicians are beginning to ask questions

Generic Versions of Toprol XL, a Heart Drug, Are Recalled

By KATIE THOMAS JUNE 23, 2014

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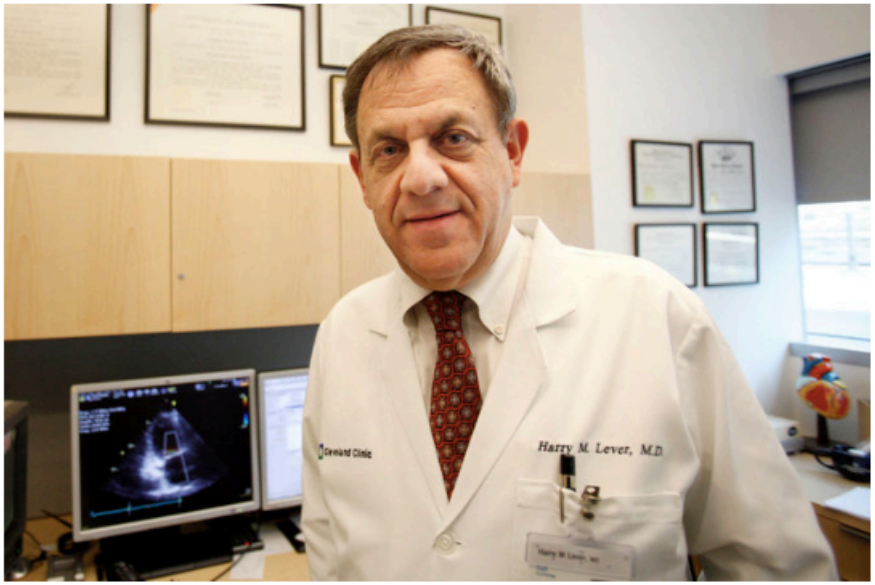
For years, Dr. Harry Lever, a cardiologist at the Cleveland Clinic, has been warning nearly anyone who would listen of his growing suspicions about generic versions of a widely used heart drug, Toprol XL.

Patient after patient, he said, would visit his office complaining of chest pains or other symptoms after switching from the brand-name version, made by AstraZeneca, to a generic product, often one made in India. When he switched them back to the brand — or to another generic — the symptoms disappeared, he said. Dr. Lever wrote a letter outlining his concerns to the Food and Drug Administration in 2012, and this year, he traveled to Washington to try to get the attention of Congress.

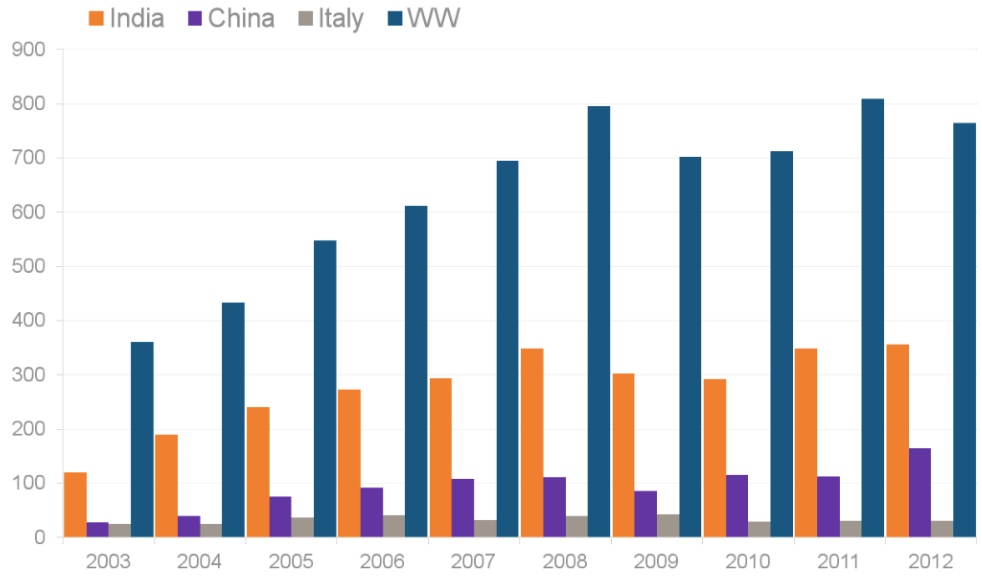
Dr. Lever could not prove that the generic drugs were to blame. "You see enough people and you get a feel, but it's anecdotes," he said in an interview Monday. "It's not science."



Dr. Harry Lever, a cardiologist at the Cleveland Clinic, said some patients taking a generic version of Toprol XL reported chest pains. David Maxwell for The New York Times

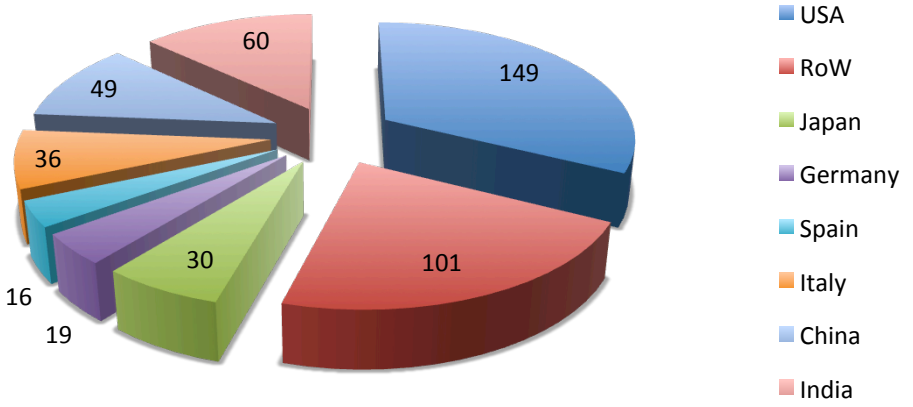
NY Times, June 23, 2014

What does this mean for China?



# of Export focussed API Manufactuters

Source: Thompson Reuters



What does this mean for China? (2)

Filler in Animal Feed Is Open Secret in China

Ariana Lindquist for The New York Times

Pieces of melamine displayed by a worker. The melamine is ground into a powder and added to animal feed as a filler to keep costs low.

By DAVID BARBOZA and ALEXEI BARRIONUEVO
Published: April 30, 2007

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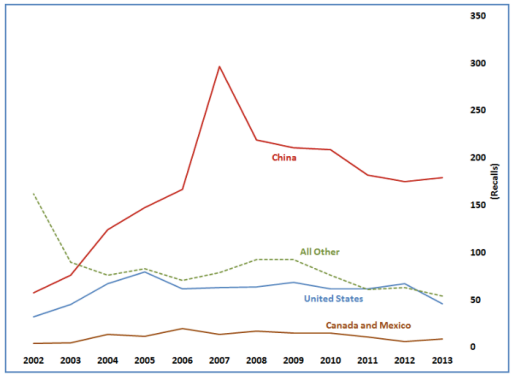
ZHANGQIU, China, April 28 — As American food safety regulators head to China to investigate how a chemical made from coal found its way into pet food that killed dogs and cats in the United States, workers in this heavily polluted northern city openly admit that the substance is routinely added to animal feed as a fake protein.

Recalls Under Consumer Product Safety Commission Jurisdiction By Country or Administrative Area of Manufacture, 2002-2013



Source: Economics and Statistics Administration analysis using data from the Consumer Product Safety Commission.

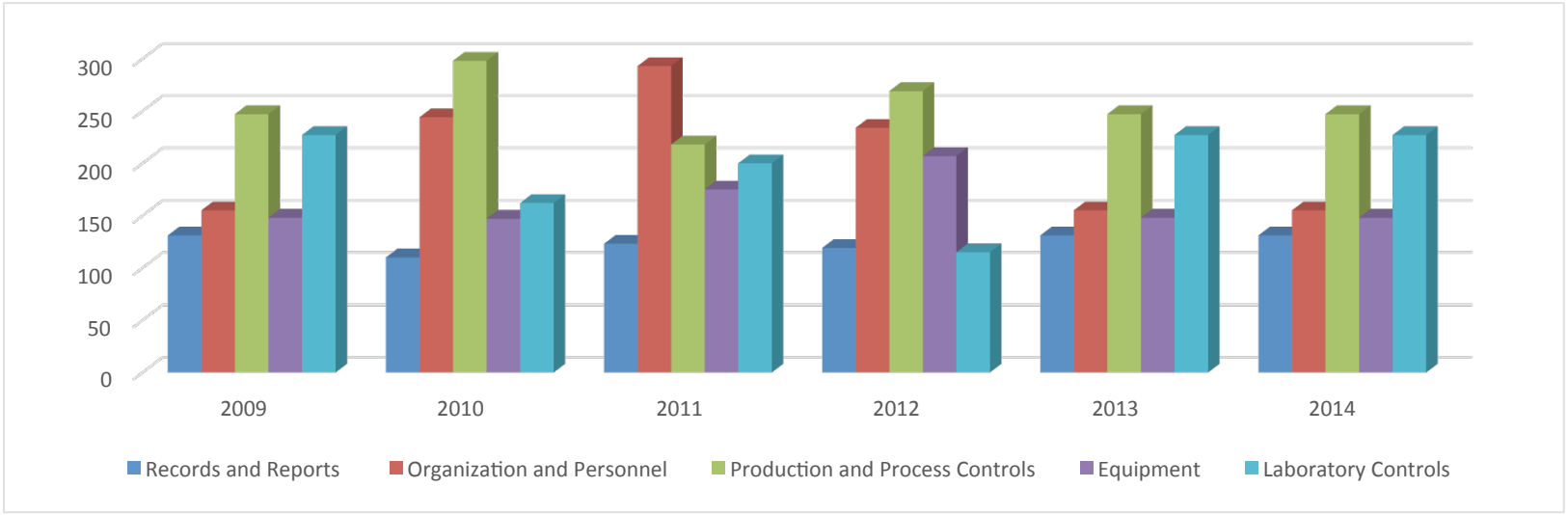
Country	# of inspections
India	111
China	111
Germany	71
Canada	46
France	43
Italy	49
Japan	47
Switzerland	36
United Kingdom	33

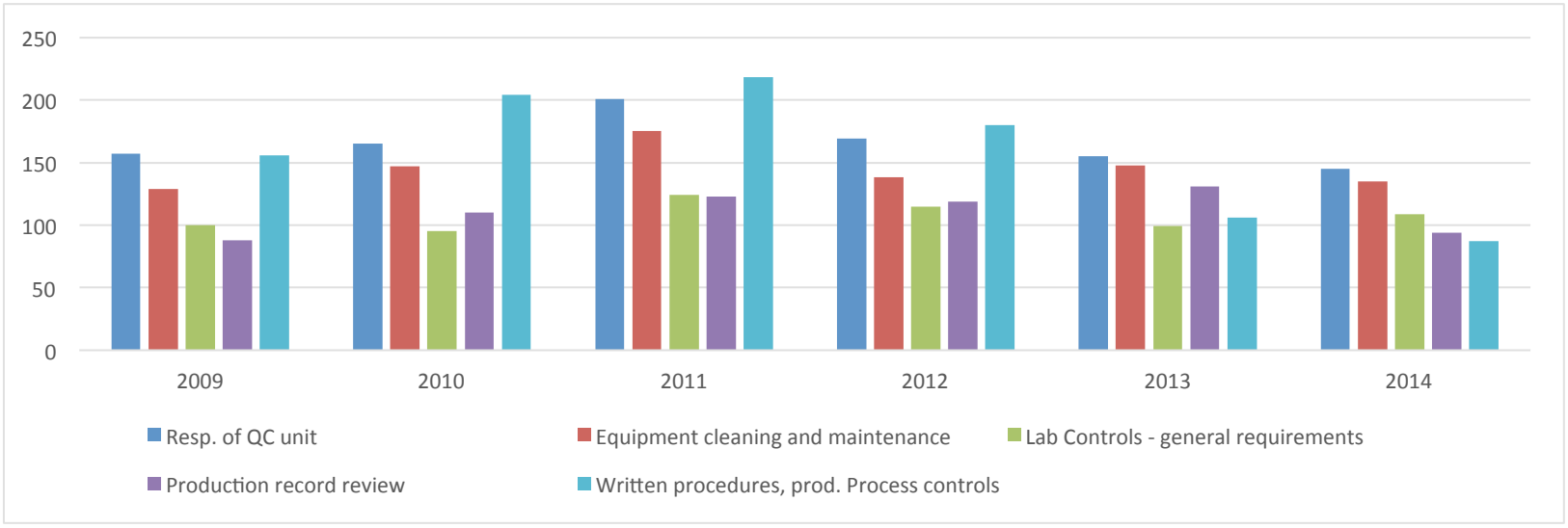
Source: US FDA, FY 2014

Our customers see this clearly

Source: "Demand Visibility Critical to Success of Healthcare and Life Science Value Chain," Gartner analysis, May 2012

Observations in during US FDA inspections





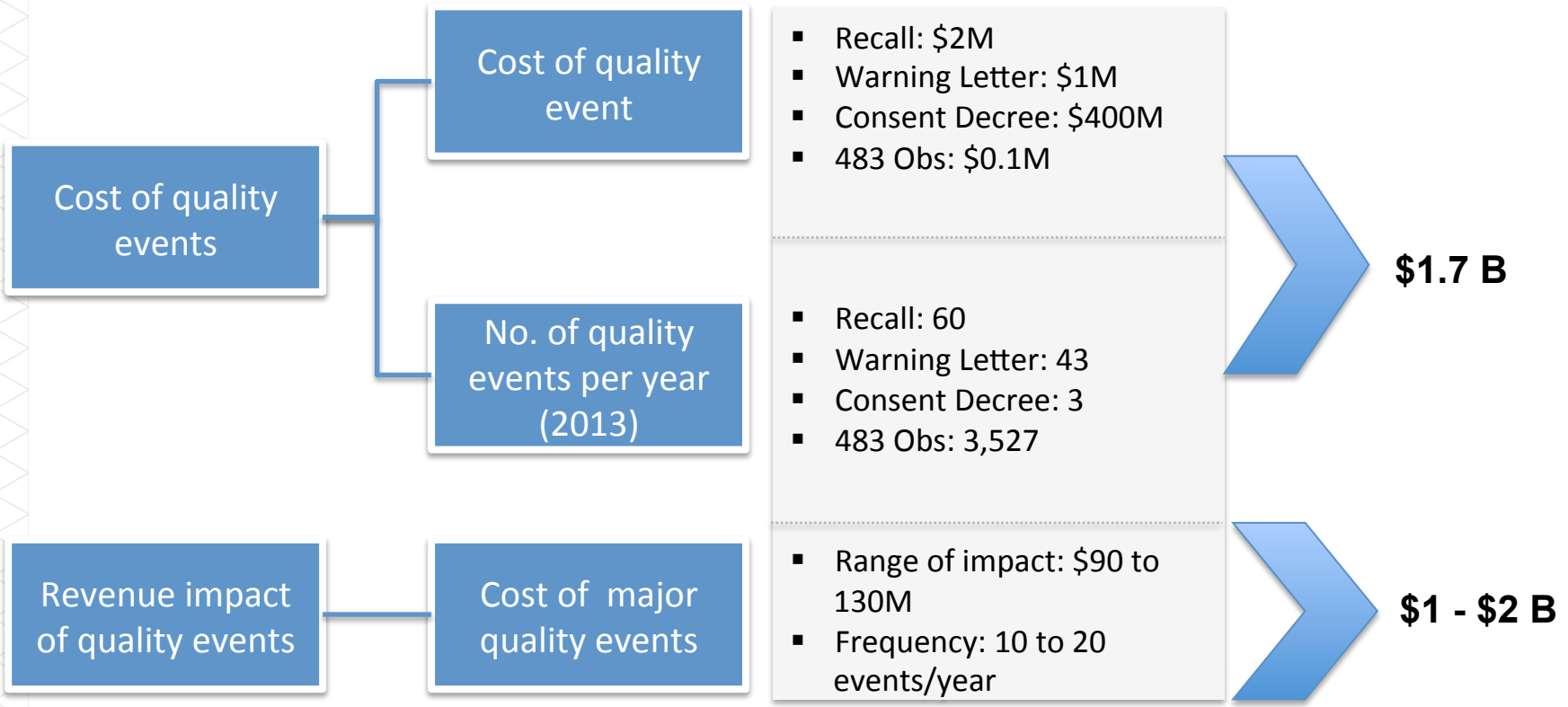
Top 5 observations on form 483 in 2014 for drugs

Number of observations	Short description
145	Procedures not in writing, not fully followed
109	Lack of scientifically sound laboratory controls
94	Lack of proper investigations of discrepancies, failures
87	Absence of written procedures
72	Written procedures not established / followed AND Inadequate procedures for sterile drug product testing

Remediation cost and revenue loss

Company	Timing	Scope	Impact	Cost / Penalty
Generics Co.	2012 - current	Manufacturing and cGMP; data integrity issues; US and India facilities	Relinquished 180 day exclusivity for three ANDA applications	• $500M in civil and criminal penalties • Up to $10M/year penalty if drugs are distributed from Consent Decree sites • Up to $30M/year penalty if additional untrue statements are made
Consumer Healthcare Co	2011 - current	Three plants in Pennsylvania and Puerto Rico	Product withdrawal & shortages; loss of market share	• $15K/day for missed commitments • $15K for each additional violation • Up to $10M files annually • Significant lost sales and incremental costs
Biotech Co	2010 - current	Fill/finish facility with contamination & cGMP issues		• Consent Decree signed in Q1 2010 • $175M disgorgement paid in Q4 2010 • $15K/day for missed deadlines
Pharma Co	2005 - current	cGMP violations and manufacturing issues	Company to recondition sized drugs	• $650M bond posted pending result of reconditioning
Pharma Co	2000 – 2006	Two facilities in NY and Pennsylvania	Sites remained open with 3rd party oversight; one of the plants was sold	• $30M in disgorgement penalty & $26 million in other fees • $267M in fines paid • Closure of two plants
Pharma Co	2002 – 2007	Facilities in Puerto Rico and NJ	Sites remained open with third party oversight	• $500M disgorgement penalty • Potential for additional $175M fines if timelines are missed • $40M in lost sales due to termination of some product lines. Approval of delayed for > 1yr

Impact of (poor) Quality on top and bottom line



- Supply chain risk events are the second largest contributors of large monthly declines in share price
- Between 2000 and 2010, an average of one major quality event per year that resulted in a 13% stock price drop across the industry

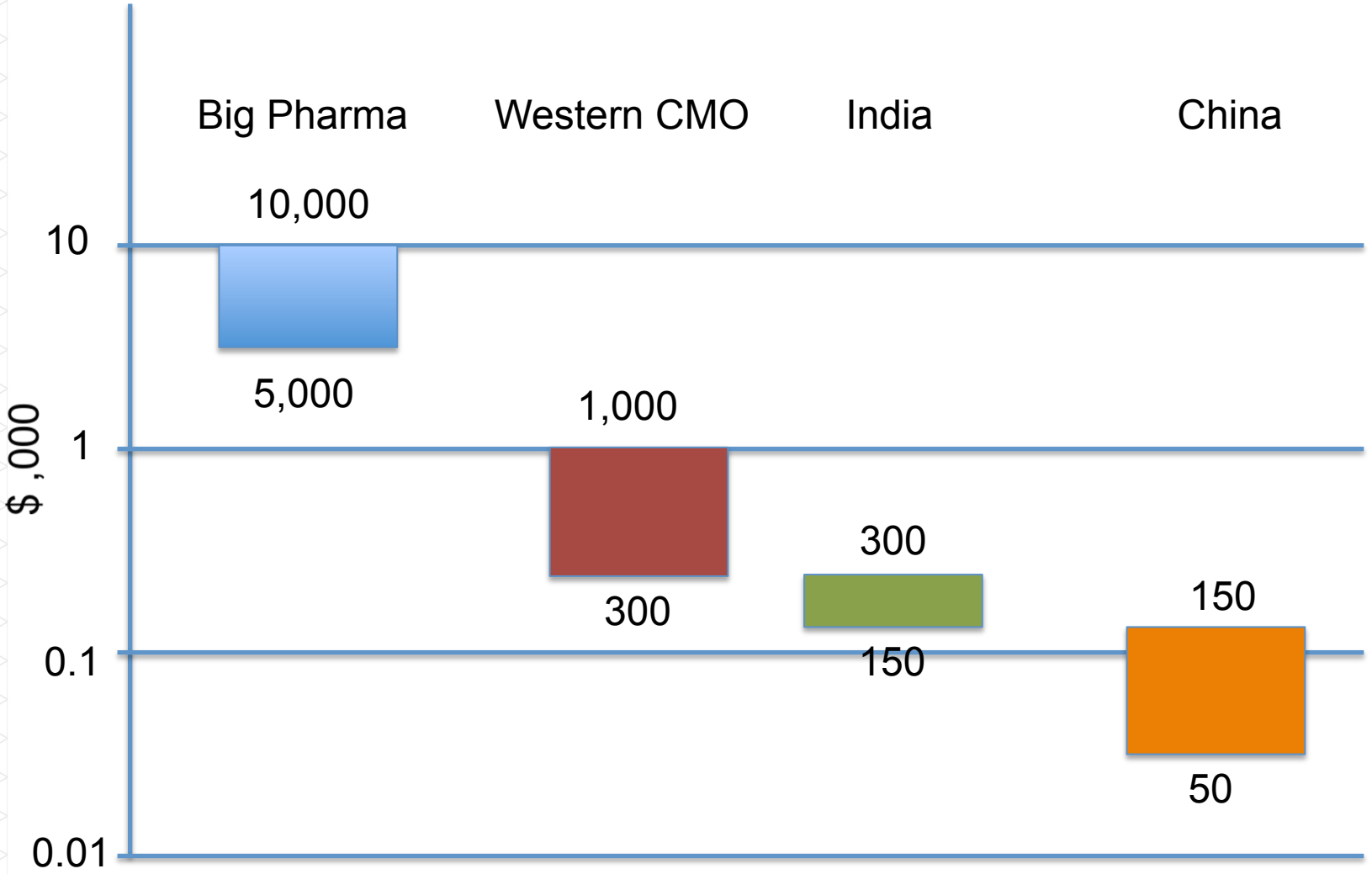
Source: FDA, McKinsey, Factiva

India and China have a significant cost advantage

Country/ Region	Labor Cost ($/ operation/ year)	Labor Productivity ($/ employee/ year)	Ratio	
			US	US =1
US	55,000	275,000	5	1
Western Europe	70,000	350,000	5	1
India	6,000	100,000	16	3
China	4,500	80,000	18	4

Fine Chemical Industry Labor Cost & Productivity comparison, 2010
Source: US Bureau of Labor & Statistics

What it takes to achieve cGMP compliance



Increased outsourcing has led to increased risk

Until recently, majority of critical components were produced internally while outsourcing was limited and capability based. Global outsourcing was typically for non-critical components.

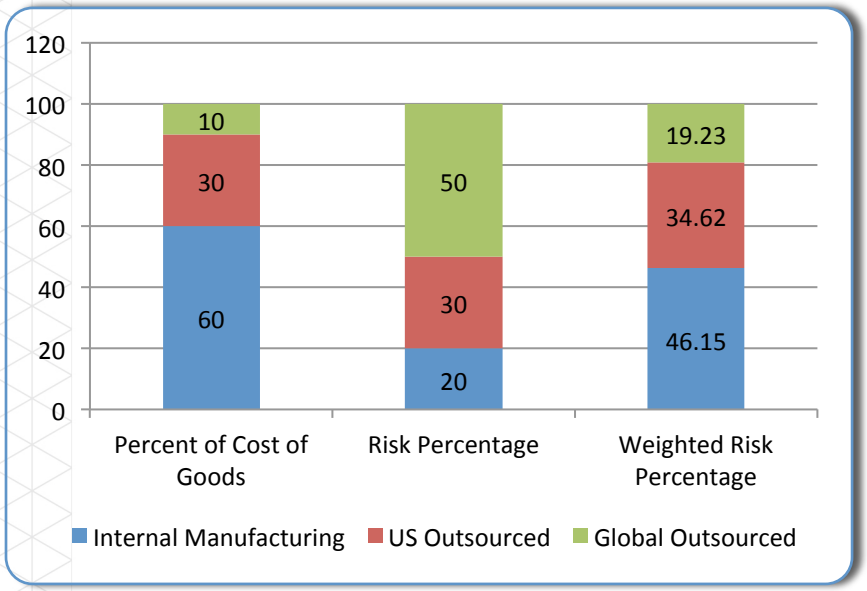
In contrast, a variety of revenue pressures have **shifted production to globally sourced** critical components (API and drug product)

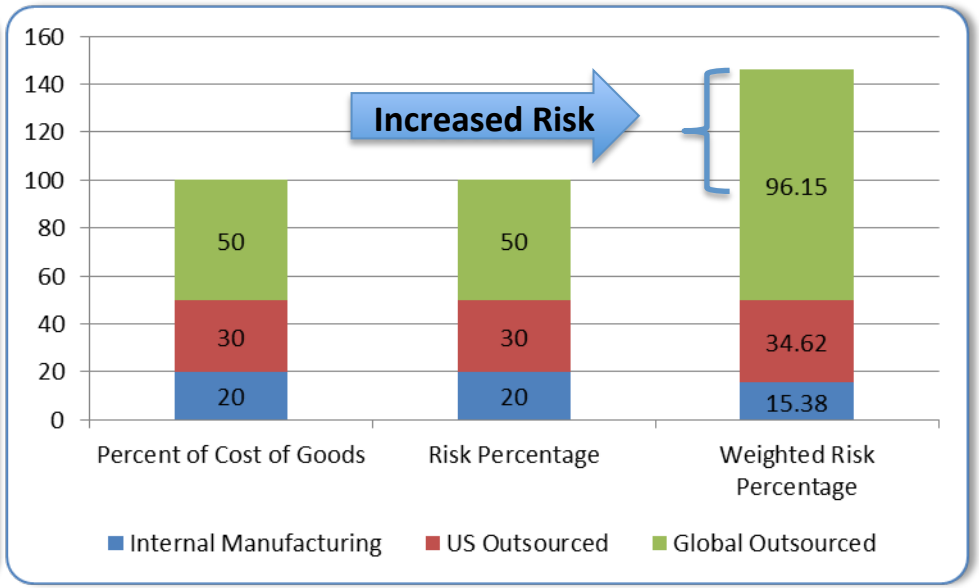
Translates

If the relative risks of the three sources of manufacturing remains same, then the **overall risk exposure increases significantly.**

Unless

There is **increased risk management** – from earlier detection through risk mitigation

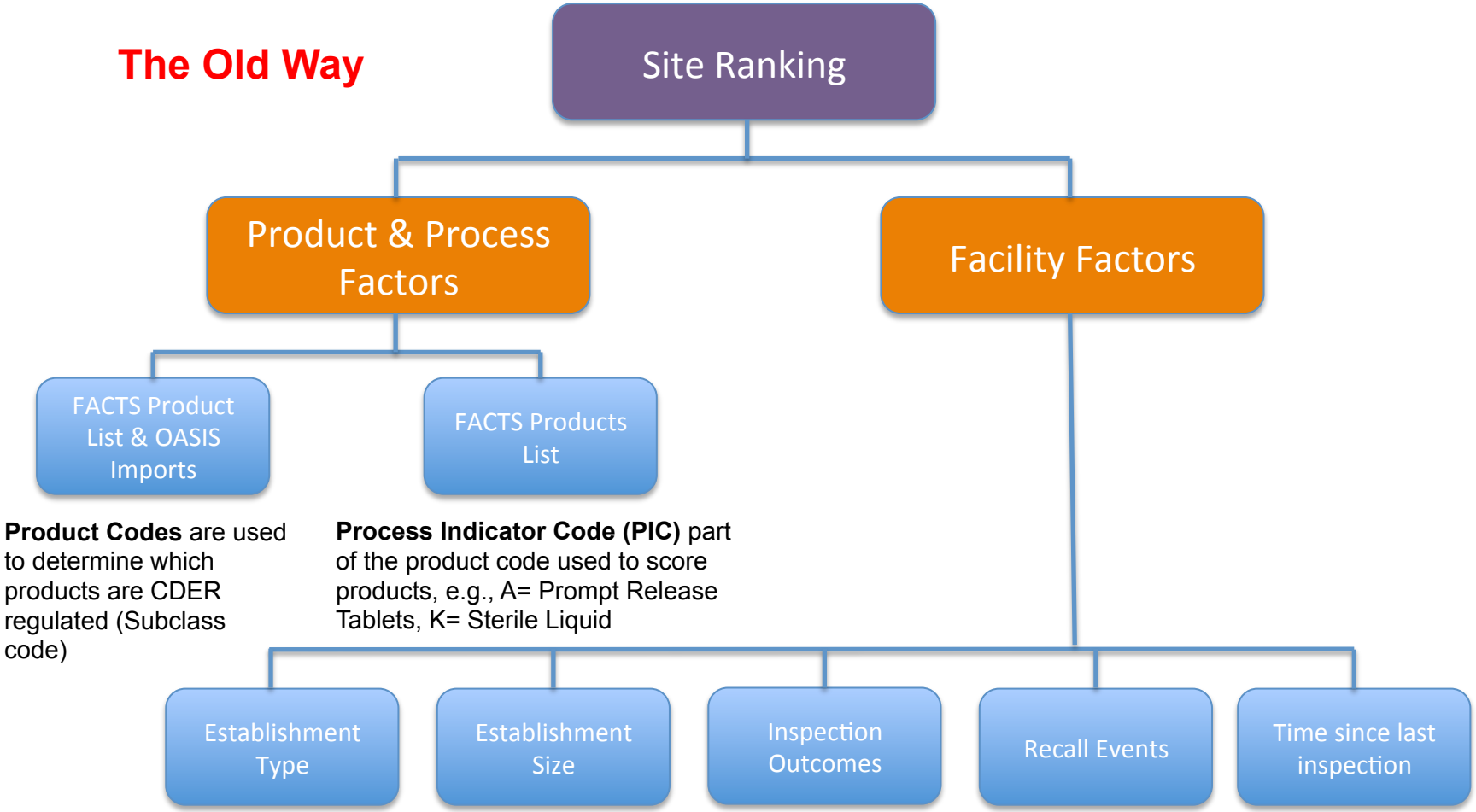




Note: Based on manufacturing and sourcing data from 30 large and mid-size pharma companies

Selection criteria for establishment inspections

The Old Way



Product Codes are used to determine which products are CDER regulated (Subclass code)

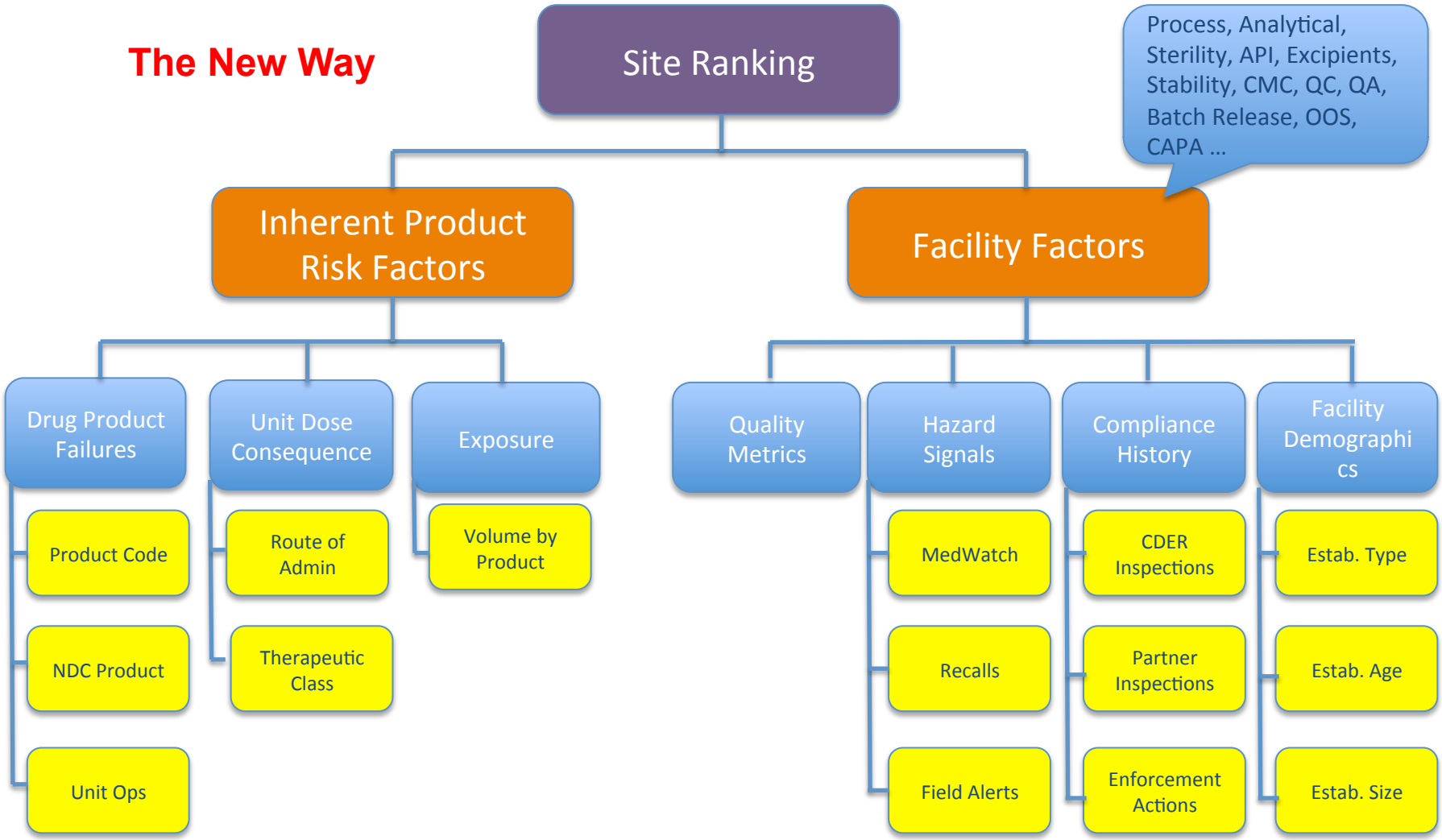
Process Indicator Code (PIC) part of the product code used to score products, e.g., A= Prompt Release Tablets, K= Sterile Liquid

Establishment Type: Manufacturers, Repackers, Control Labs etc.
Establishment Size: Proxy for measuring exposure
History of inspection outcomes : NAI, VAI or OAI
Number of recalls in last three years: Class I, Class II, Class III

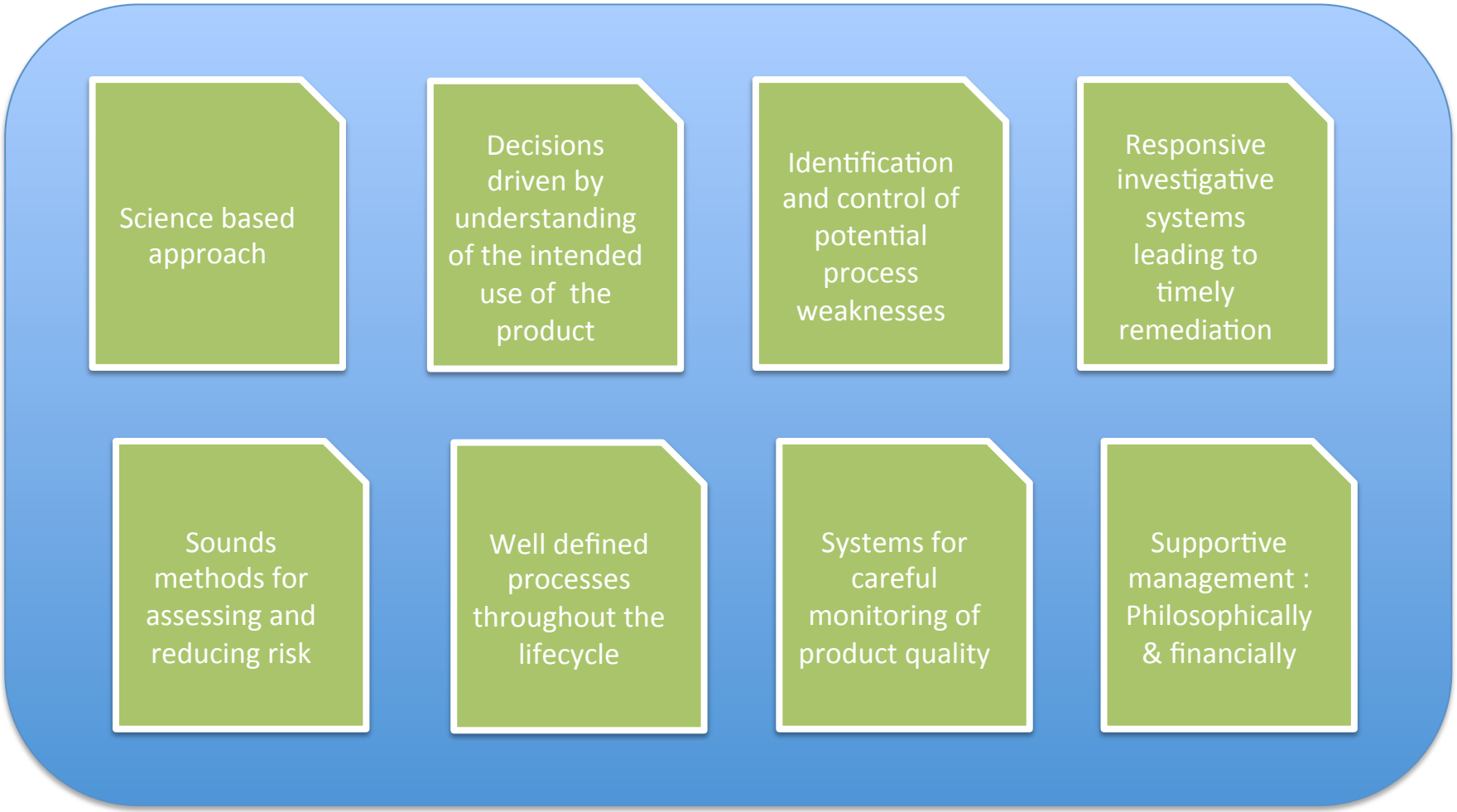
FDASIA Section 705: Risk-Based Inspection Frequency

- Risk Factors: In establishing the risk-based scheduled under paragraph (3), the Secretary shall inspect establishments according to the known safety risks of such establishments, which shall be based on the following factors:
  - Compliance history of the establishment
  - The record, history and nature of recalls linked to the establishment
  - The inherent risk of the drug manufactured, prepared, propagated, or compounded at the establishment
  - The inspection frequency and history of the establishment, including whether the establishment has been inspected pursuant to section 704 with the last 4 years
  - Whether the establishment has been inspected by a foreign government or an agency of a foreign government under section 809
  - For any other criteria deemed necessary and appropriate by the Secretary for the purposes of allocating resources

Selection criteria for establishment inspections



8 Pillars of an effective Quality System



Source: Guidance for the industry: Quality systems approach to Pharmaceutical cGMP Regulations, 2006

What do you look for in "Quality Culture"

Beliefs & Behaviors	Quality & Compliance indicators
<u>Belief</u> *Cost efficiencies through operational excellence* <u>Behavior</u> *Financial targets are addressed through continuous improvement initiatives*	• Reduction in waste/scrap • Improved cycle times • Efficiencies in operational cost • Right first time
<u>Belief</u> *Deviations are learning experiences to address root causes that can compromise operational excellence* <u>Behavior</u> *Investigate to identify and correct root cause vs. investigate to release the lot*	• Deviation metric- reduction of repeat deviations • CAPA effectiveness • # of on-going Continuous improvement initiatives

What do you look for in "Quality Culture"

Beliefs & Behaviors	Quality & Compliance indicators
<u>Belief</u> *Our primary responsibility is to our customers, consumers and patients* <u>Behavior</u> *Market surveillance activities do not compete with making and releasing lots to market* *Defining own internal standards vs. merely complying to FDA requirements*	• Review, investigation and management of customer complaints executed in a timely manner • Timely reporting to FDA and market action when required. • On time stability testing • Critical to quality process parameters are well defined and monitored • Risks are known and mitigation plans are in place • Reduced number of market actions
<u>Belief</u> *Management views product quality as a business imperative.* <u>Behavior</u> *Management gets involved and seeks to understand site challenges through governance forums*	Product quality issues/constraints become business priorities and are resourced to be addressed in timely manner, favorably impacting: • Product approval rate • Customer complaint rate

Elements of Data Integrity

Parameter	Description
Accurate	No errors or editing without documented amendments
Attributable	Who acquired the data or performed an action and when?
Available	For review and audit or inspection over the lifetime of the record
Complete	All data is present and available
Consistent	All elements of the record, such as the sequence of events, follow on and are dated or time stamped in expected sequence
Contemporaneous	Documented at the time of the activity
Enduring	On proven storage media (paper or electronic)
Legible	Can you read the data?
Original/Reliable	Written printout or observation or a certified copy thereof
Trustworthy	The data and the record have not been tampered with

Breaches of data integrity (BDI) are acts of "falsification, document adulteration, forgery and providing misleading information" - Carmelo Rosa, Director, CDER Office of Compliance*

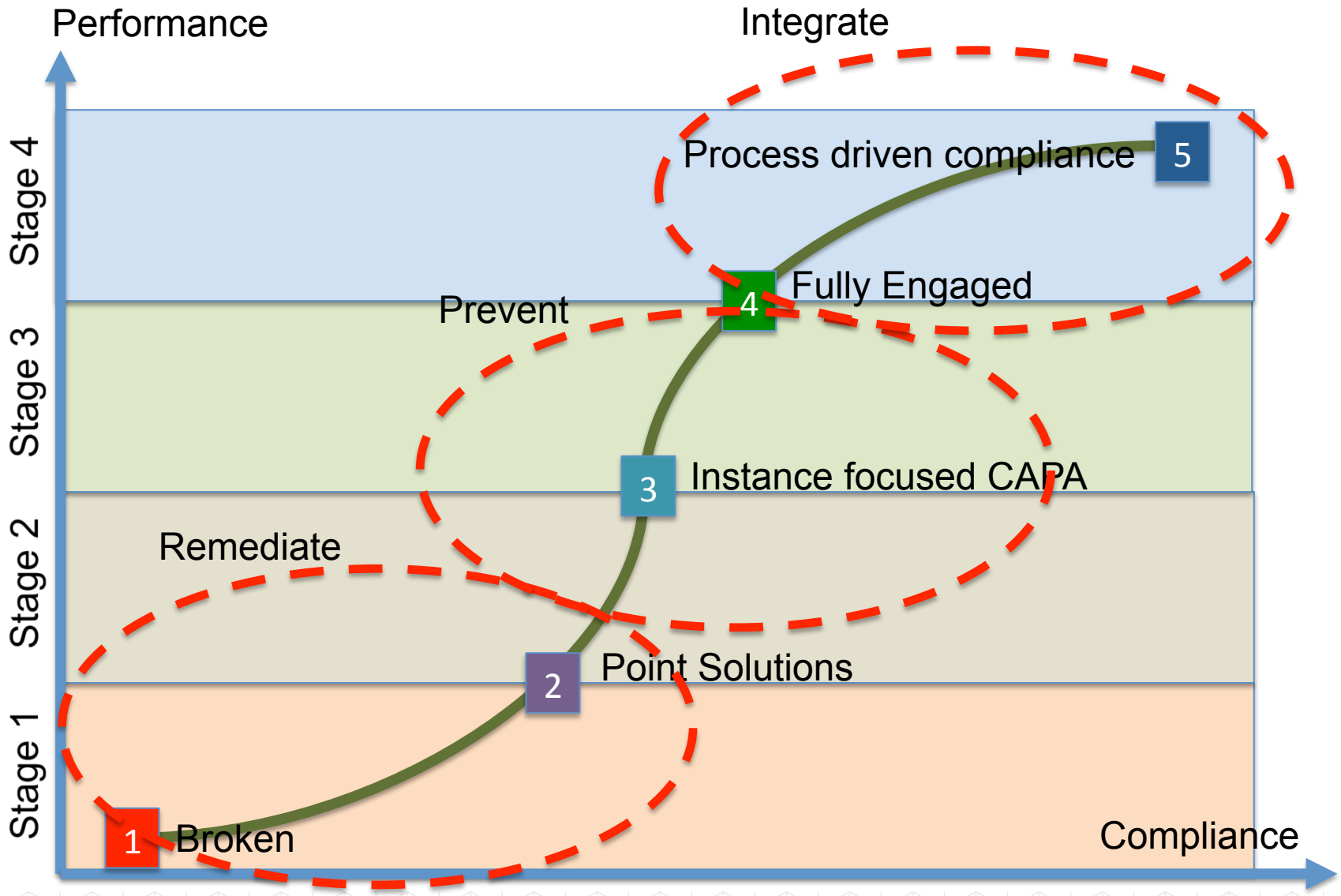
MHRA guidelines for Data Integrity: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/412735/Data_integrity_definitions_and_guidance_v2.pdf

Source: R.D. Mcdowall, Spectroscopy, Focus on Quality, December 2010

Data Integrity – Best practices

Ensuring Data Integrity	
Embed data integrity verification activities into internal audit processes	Train your internal auditors to understand what to look for when detecting data integrity deficiencies
Create awareness among staff so they can assist with this endeavor, and report concerns before they become full-fledged issues	Seek external support to assure completely unbiased, third-party investigations and/or to enhance your internal investigation program

Compliance Maturity Curve



Quality control at Chinese manufacturers

- There is much reliance on testing the product according to the pharmacopeia
- Testing is not always suitable to the manufacturing process, as pharmacopoeias cannot keep up with new processes
- Residues of solvents and potentially genotoxic catalysts are rarely controlled
- Impurity profiles are seen in only 6% of our audits

Source: Supervision of Chinese-made drug substance, Philippe Andre, Qualiau Pharmaceutical Auditing Co., Ltd.

Thank you

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www.medassurecompliance.com

Appendix

Data Integrity during active usage

Example Considerations:

- Have personnel been trained on good documentation and good data integrity practices
- How does the firm ensure that analysts enter ALL test data, not just the passing test results?
- For transcribed data, what verification processes are in place?
- When data is scanned, how does the firm ensure the evidentiary admissibility of the scan (e.g., "certified copy")?
- Has the system been validated and under change control?

Data Integrity during active usage

Example Considerations:

- Did the firm verify computerized calculations prior to usage on the data?
- Does the firm claim to use "paper records only" but then actively use e-records to release batches, make safety and efficacy decisions, etc.?
- How does the firm ensure that previously recorded SUSAR data cannot be altered when reviewed?

Data Integrity during active usage

Example Considerations:

- Does the firm retain raw lab data/digital clinical source data along with context (e.g., metadata)?
- What were the process checks undertaken prior, during, and after clinical trial database lock? Transmittal to the sponsor
- Does the firm have traceability on its complaint records to ensure that none of the data is left out of any later analysis (such as for an APR or QSMR) or when transmitted?

Data Integrity during active usage

Example Considerations:

- If the firm uses a storage vendor, is the vendor qualified?
- How often does the firm sample its long-term archives to ensure continuing storage suitability and prevent data deterioration?
- What controls does the firm have on retained record destruction to prevent inadvertent loss of required data?
- Does the firm have a digital media migration strategy?

Identifying "Data Integrity" issues

- HPLC processing methods (including integration parameters) and re-integrations are executed without a pre-defined, scientifically valid procedure
- Testing samples unofficially, and not reporting all results obtained. Specifically, "test," "trial" and "demo" injections of intermediate and final API samples were performed, prior to performing the tests that would be reported as the final QC results.
- "When weighing samples, reagents, and other laboratory materials, QC analysts write weight values on small pieces of paper, transcribe the values onto the analytical worksheets, and then destroy the original paper on which the weights are written."
- Failure to review and investigate production and QC laboratory deviations

Identifying “Data Integrity” issues

- Out-of-specification or undesirable results were ignored and not investigated
- Samples were retested without a record of the reason for the retest or an investigation. Only passing results were considered valid, and were used to release batches of APIs intended for US distribution
- During the inspection, management acknowledged that the some of the chromatograms observed were related to the practice of blending an API batch that failed to meet specifications with an API batch that passed specifications. The combined batch was retested and distributed using the new acceptable Quality Control results.

Identifying "Data Integrity" issues

- The audit trail function for the chromatographic systems was disabled at the time of the inspection
- Failure to protect computerized data from unauthorized access, changes, or deletion
    - No computer lock mechanism had been configured to prevent unauthorized access to the operating system
- QC laboratory personnel shared the same username and password for the operating systems and analytical software on each workstation in the QC laboratory