Path to Rational Quality Assurance

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This talk

Reflections and projections

- Human behavior & 'intention – implementation' gaps
- FDA's initiative on 'Pharmaceutical cGMP's for the 21st Century – A Risk Based Approach'

Deputy Assistant Attorney General Maame Ewusi-Mensah Frimpong (January 29, 2013)

- *"In addition to focusing on plants and production lines and manuals and policies and testing and controls, I urge you to also focus on people. People are at the heart of what you do, and it is the failures of people—often the combined failures of a number of people—which result in noncompliance. Therefore, in our investigations, we are looking at people to determine responsibility. And for this same reason, we urge you to look at people."*

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)

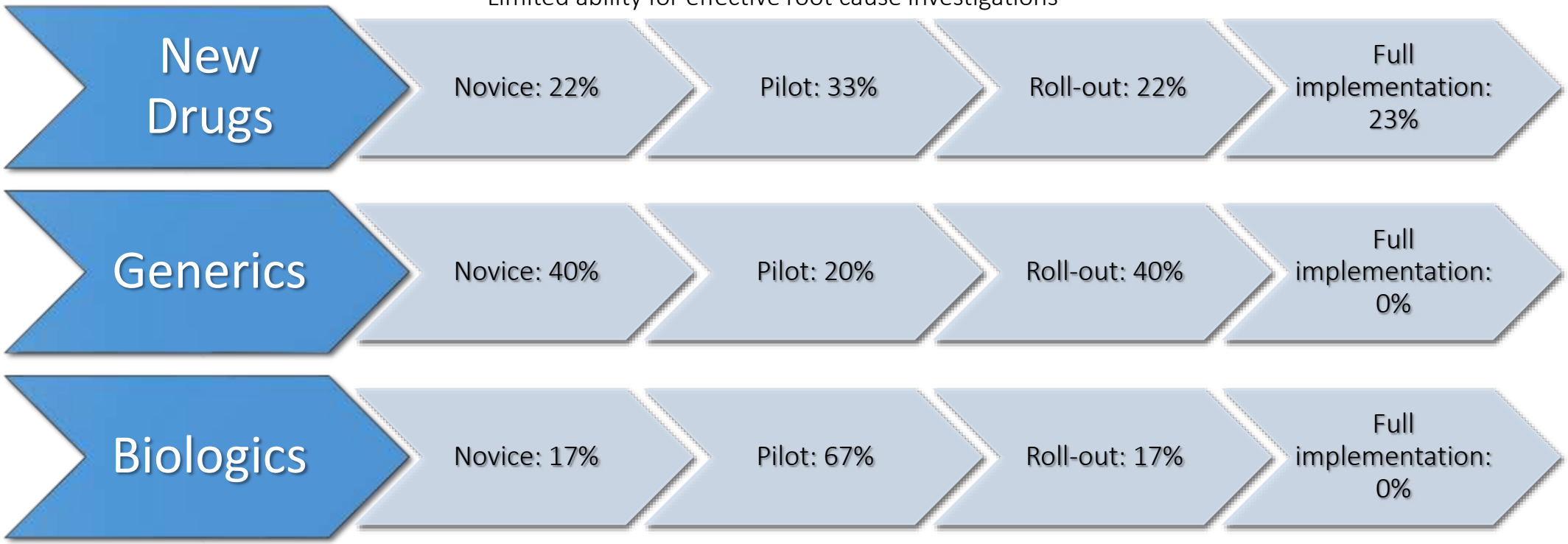
Quality can not be tested into products, it has to be built-in by design

FDA's Initiative on Pharmaceutical Quality for the 21st Century

A decade ago	FDA Science Board Review	FDA's PAT Team	PAT, ICH Q8, 9, 10,… Process Validation	Current state (today)
Drug shortages, WL, consent decrees,…	"Don't use - don't tell"; Poor efficiency, root cause unknown	Additional organizational changes – (CMC + cGMP)	Science based controls, measurements for material attributes; risk-based decisions.	Drug shortages, WL, consent decrees,..

Current state of QbD implementation

Limited ability for effective root cause investigations



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

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"

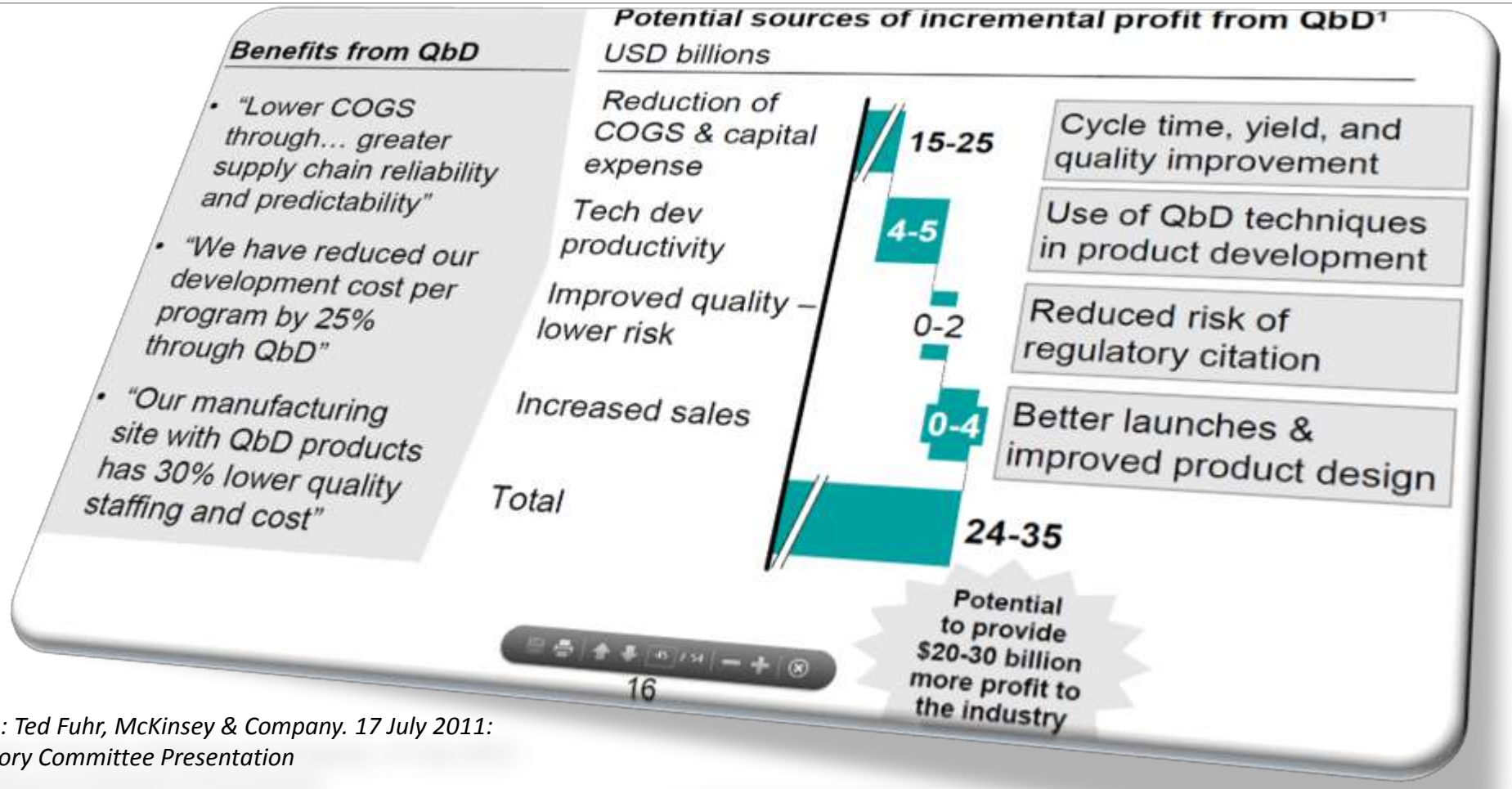
Challenges

(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

Benefits reported and calculated



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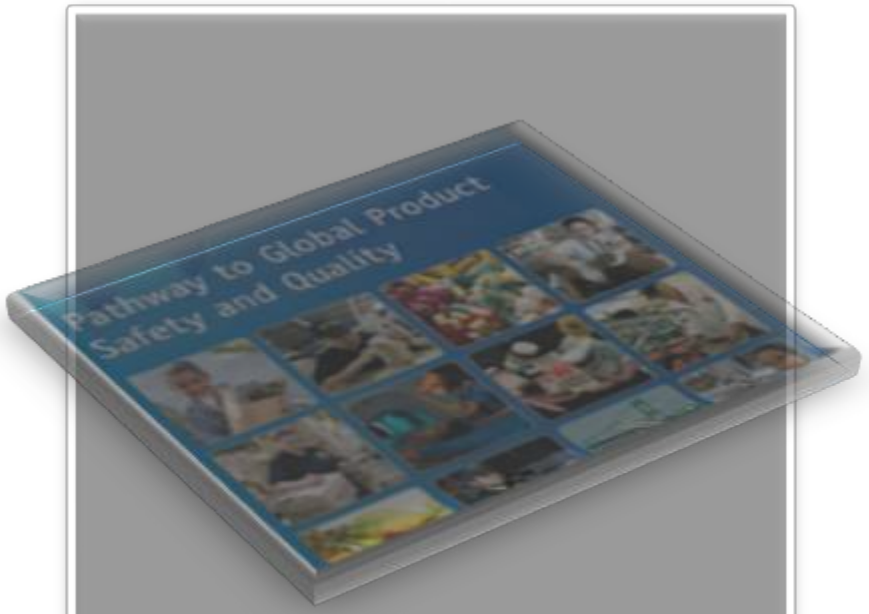
GXP's – issues increasing globally

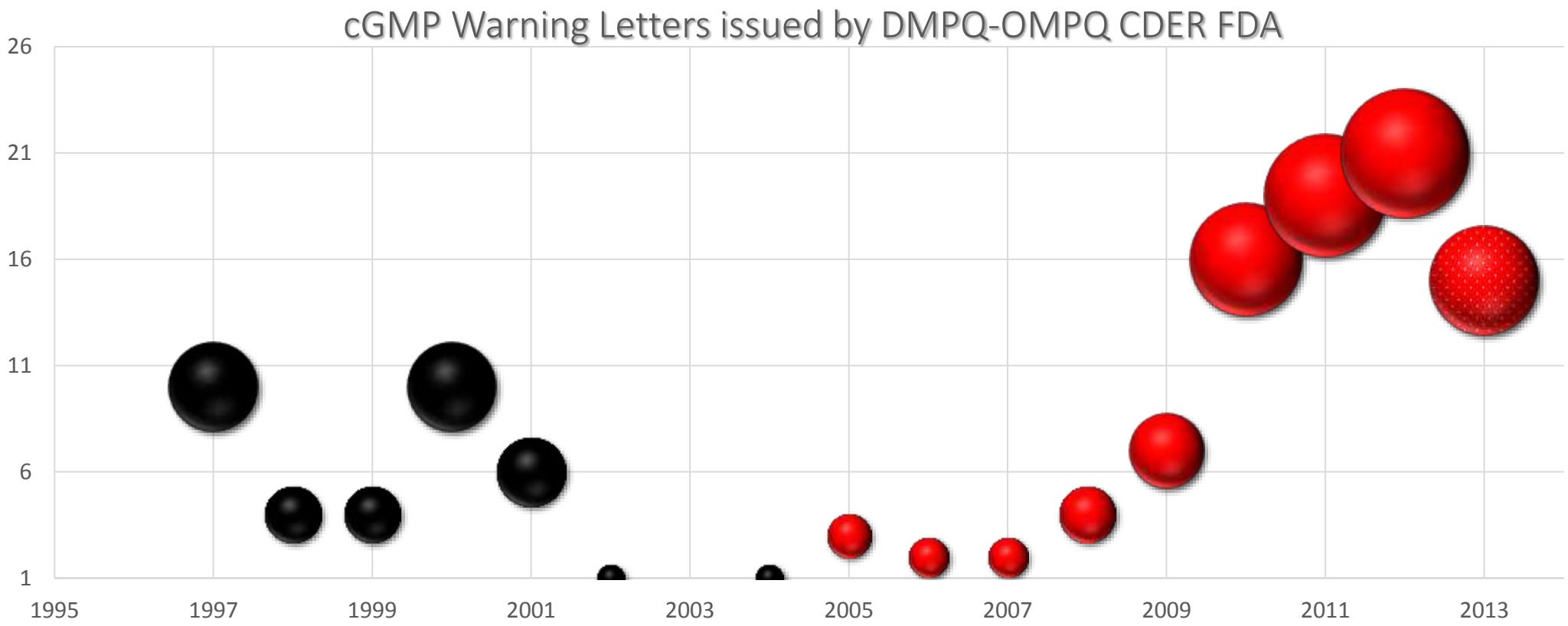


FDA - several warning letters in 2011 and 2012 in China, Mexico, UAE, Canada and the US

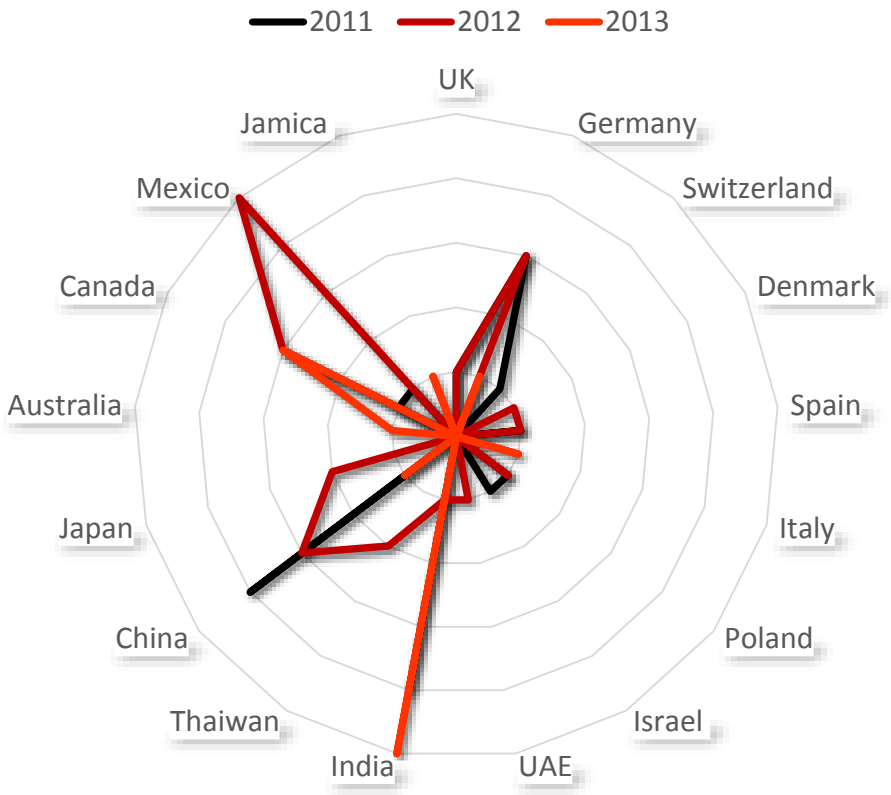
In 2013 several companies in India receive GMP warning letters

Just as diseases know no borders, in today's globalized world, product safety and quality know no boundaries. Stronger regulatory systems overseas mean safer products at home. - See more at:

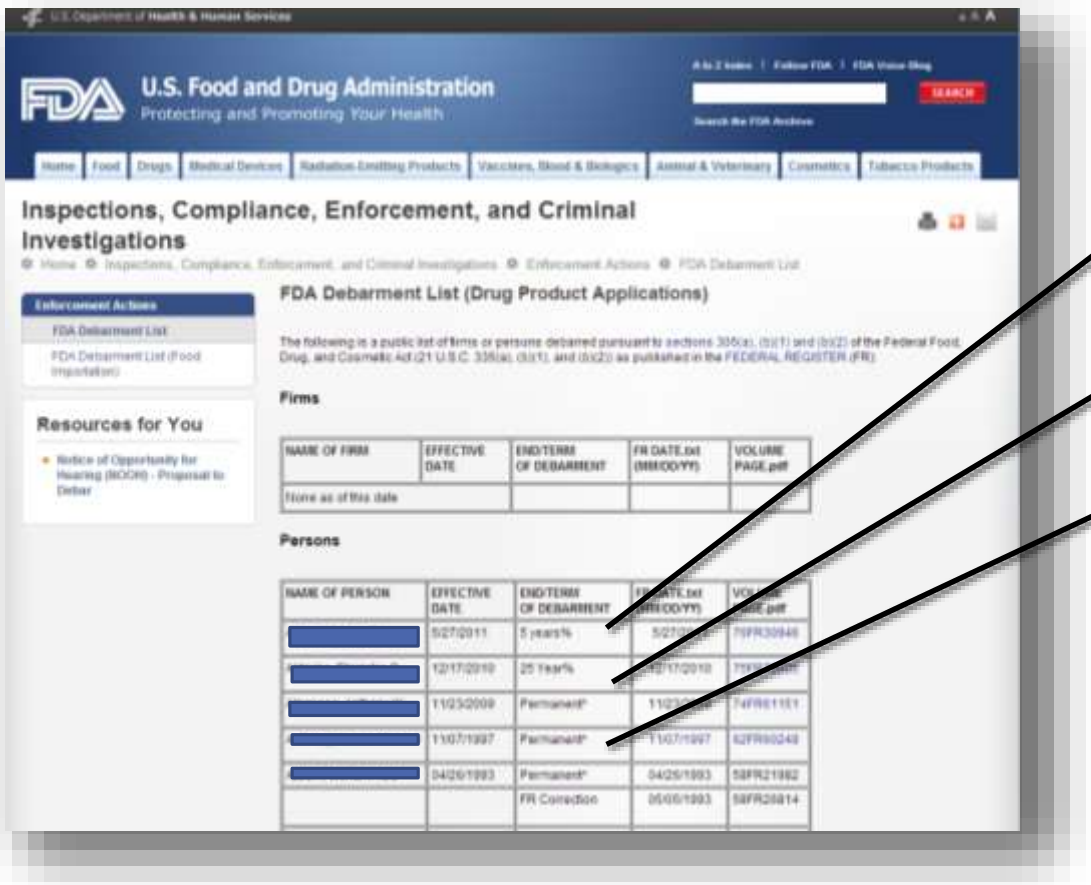
Increasing frequency of FDA inspections
(Foreign Facilities)



FDA CDER Warning Letters 2011-2013 (August)



When conduct becomes a crime



5 years

25years

Permanent

FDA's Office of Criminal Investigations

- Different from, but enhances, the regulatory inspectors and investigators
- Unique fact-finding tools and provide for strong, industry-wide deterrence

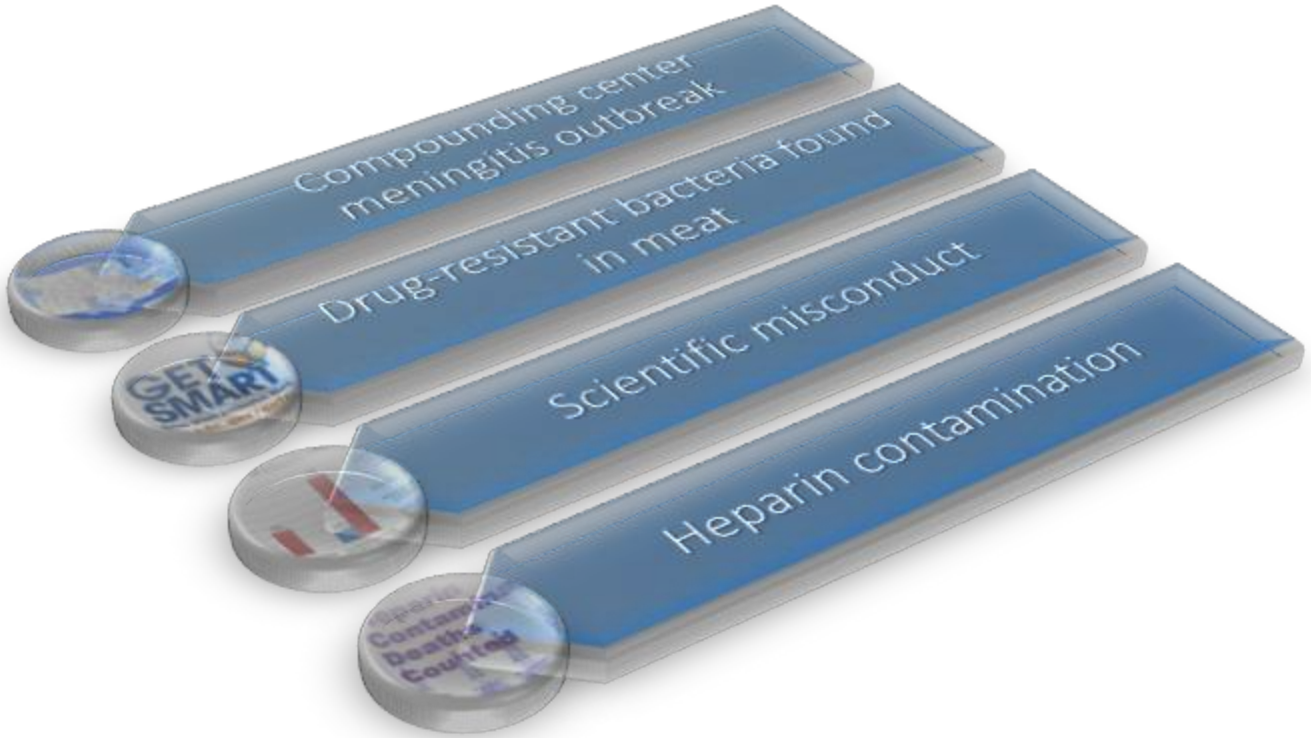
Department of Justice's [new] tools…

"CIA"…Compliance Officer,…Board obligations

"IRO".. Independent review of systems, processes, policies, and procedures

Are intended to change behavior

Conduct becomes a crime because - humans are predictably irrational



‘The (Honest) Truth about Dishonesty’

Dan Ariely, a professor of psychology and behavioral economics at Duke University

“very few people lie a lot, but almost everyone lies a little”

"We want to view ourselves as honest, wonderful people and when we cheat ... as long as we cheat just a little bit, we can still view ourselves as good people”

“if we get one person to cheat in an egregious way and other people see them, they start cheating to a higher degree.”

The traditional cost/benefit theory of dishonesty

"Not only is it a bad descriptor of human behavior, it's also a bad input for policy.”

“When we try to curb dishonesty in the world, what do we do? We get more police force, we increase punishment in prison.”

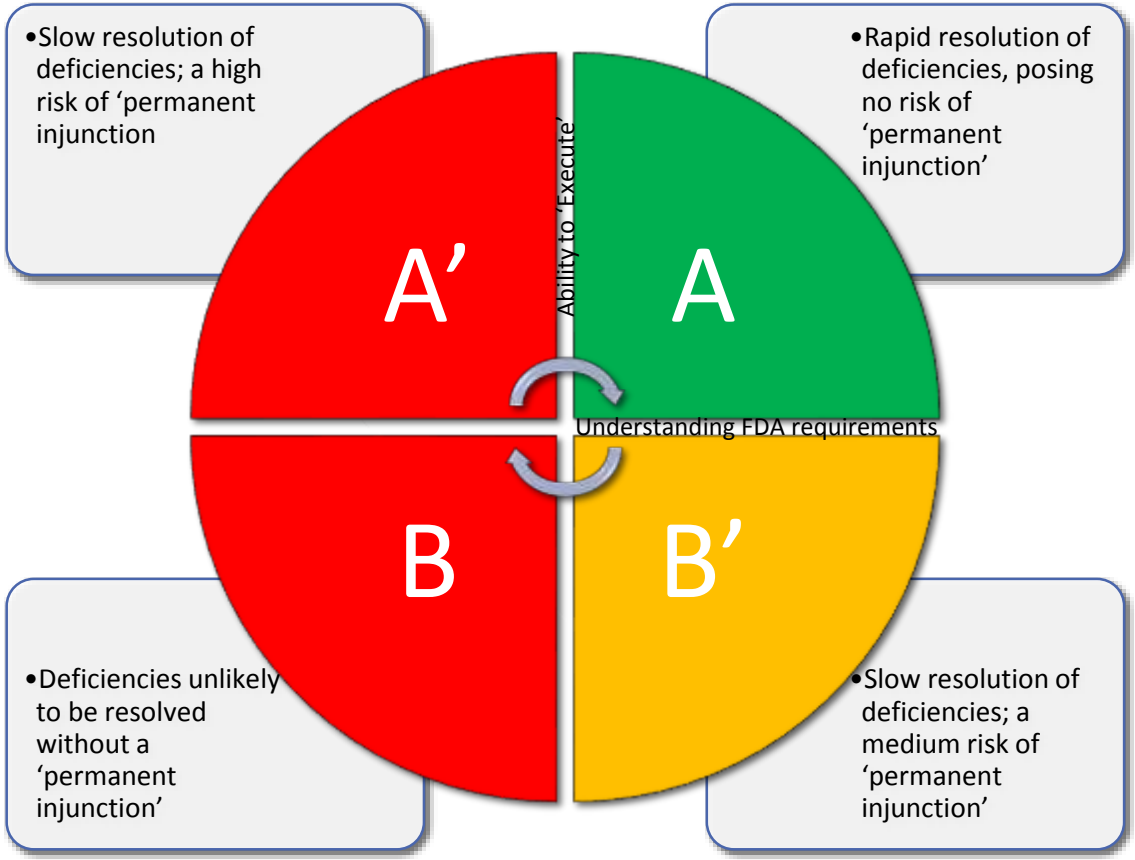
“If those are not the things that people consider when they think about committing a particular crime, then all of these efforts are going to be wasted.“

Perspectives from outside and afar

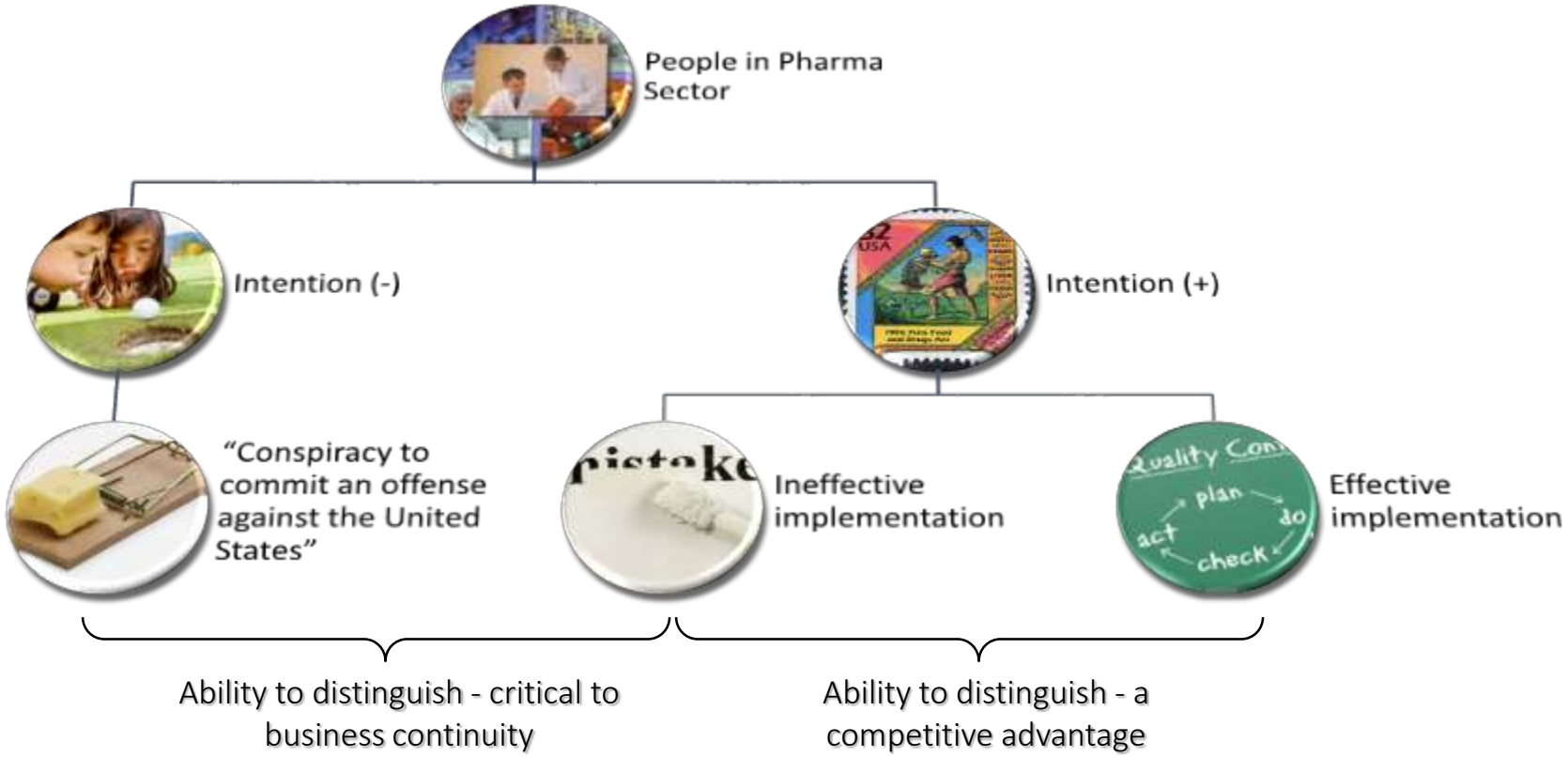
"Unlike the FDA, .., which forces medical practitioners and pharmaceutical companies to test their assumptions before sending treatments into the marketplace, no entity requires business (and also the public sector) to get at the truth of things." Dan Ariely, Harvard Business Review July–August 2009

"The notion 'by design,' in the phrase 'Quality by Design,' conveys the intention to deliver a product or service with a pre-defined 'quality' so as to satisfy intended customers." Ajaz S. Hussain. SWISS PHARMA 34 (2012) Nr. 6.

Ideally rapid resolution and no risk of *permanent injunction*



Distinguishing between cognitive biases & cheating by design



A few facts about cGMPs …from FDA

Consumers expect that each batch of medicines they take will meet quality standards so that they will be safe and effective

While cGMPs require testing, testing alone is not adequate to ensure quality.

It is important …. to assure that quality is built into the design and manufacturing process at every step.

If a company is not complying with cGMP regulations, any drug it makes is considered “adulterated” under the law.

A few facts about cGMPs …from FDA

This kind of adulteration means that the drug was not manufactured under conditions that comply with cGMP

It does not mean that there is necessarily something wrong with the drug.

A very expensive confusion….

In 2010 a British drugs giant paid £475million to settle allegations it knowingly made and sold adulterated drugs.

A payment of £60million to a former employee who alerted the authorities

More recently, in announcing a consent decree against an Indian company DOJ [Dept. of Justice] called the move unprecedented – "groundbreaking in its international reach."

In a report dated 26 August 2013 the CEO of this Indian Company explained…

"The meaning of the word adulterated was very different in the US compared to the dictionary meaning as understood by people or even as defined under the Indian Drugs and Cosmetics Act."

Catastrophic risk for the company

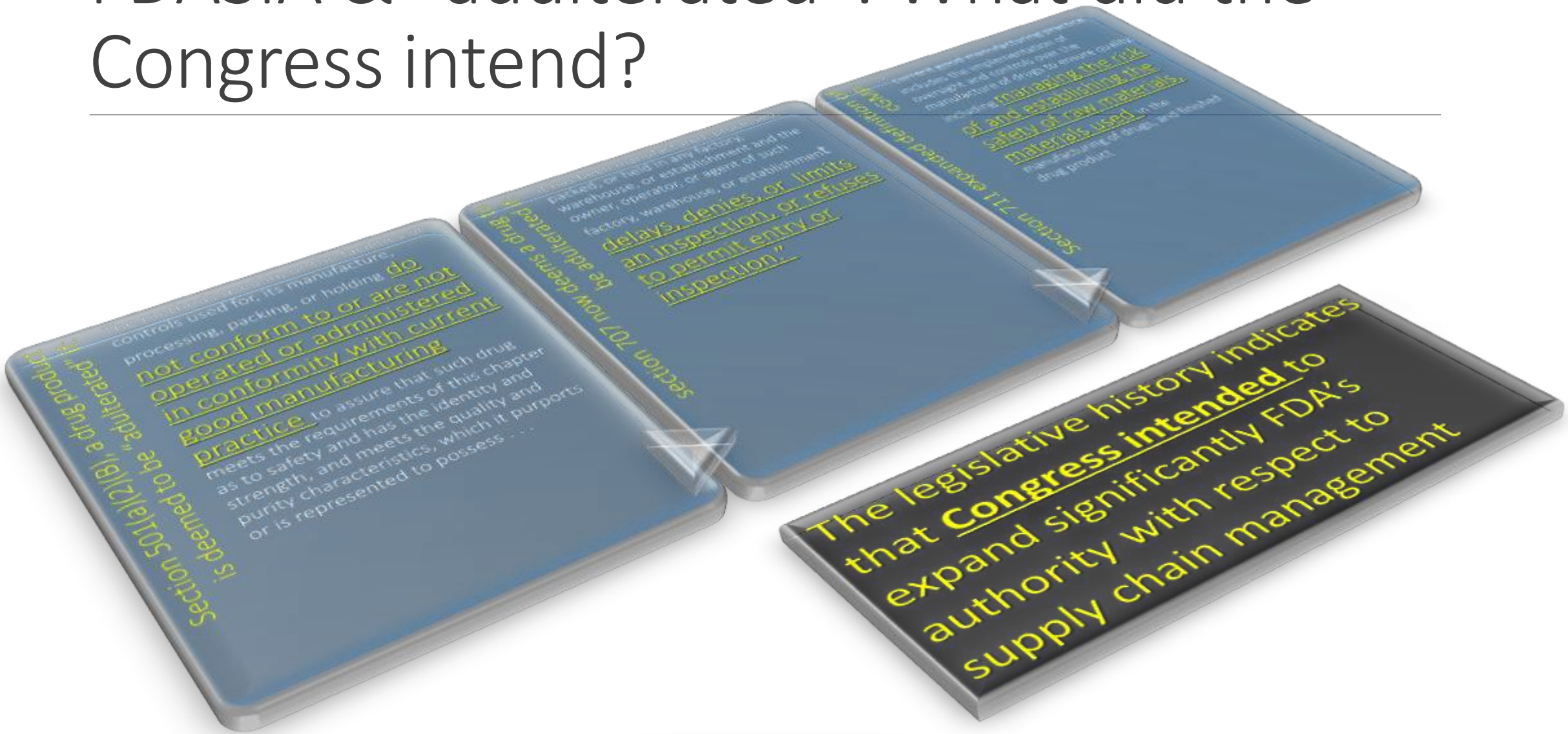
Often difficult to address customers directly

Shareholders likely to fault the board

"Quality is made in the Board Room" Deming

Courts often agree

FDASIA & “adulterated”: What did the Congress intend?



Or simply strengthening FDA's authority?

Companies are responsible for delivering quality products

- This entails understanding and controlling sources of variability in materials, suppliers, environments,… and people

Delaying, denying or limiting an inspection - is it not an irrational behavior?

- Each day a facility is in operation it is open for inspection; elaborate preparations are unnecessary for an [FDA] inspection

FDASIA - additional requirements?

Or simply strengthening FDA's enforcement authority?

FDA's PAT Guidance

A process is generally considered well understood when:

Companies whose intention has been to achieve and delivery quality by design; would have an adequate level of process understanding; at minimum (1) & (2)

(1) all critical sources of variability are identified and explained;

(2) variability is managed (controlled) by the process; and,

(3) product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, manufacturing, environmental, and other conditions.

Can it serve as a pretext to ‘rationalize’ deliberate non-compliance?

“Conspiracy to commit an offense against the United States” & “duping the FDA for six years.”

FDA 483 (05/02-07/01/2005): 12 Observations

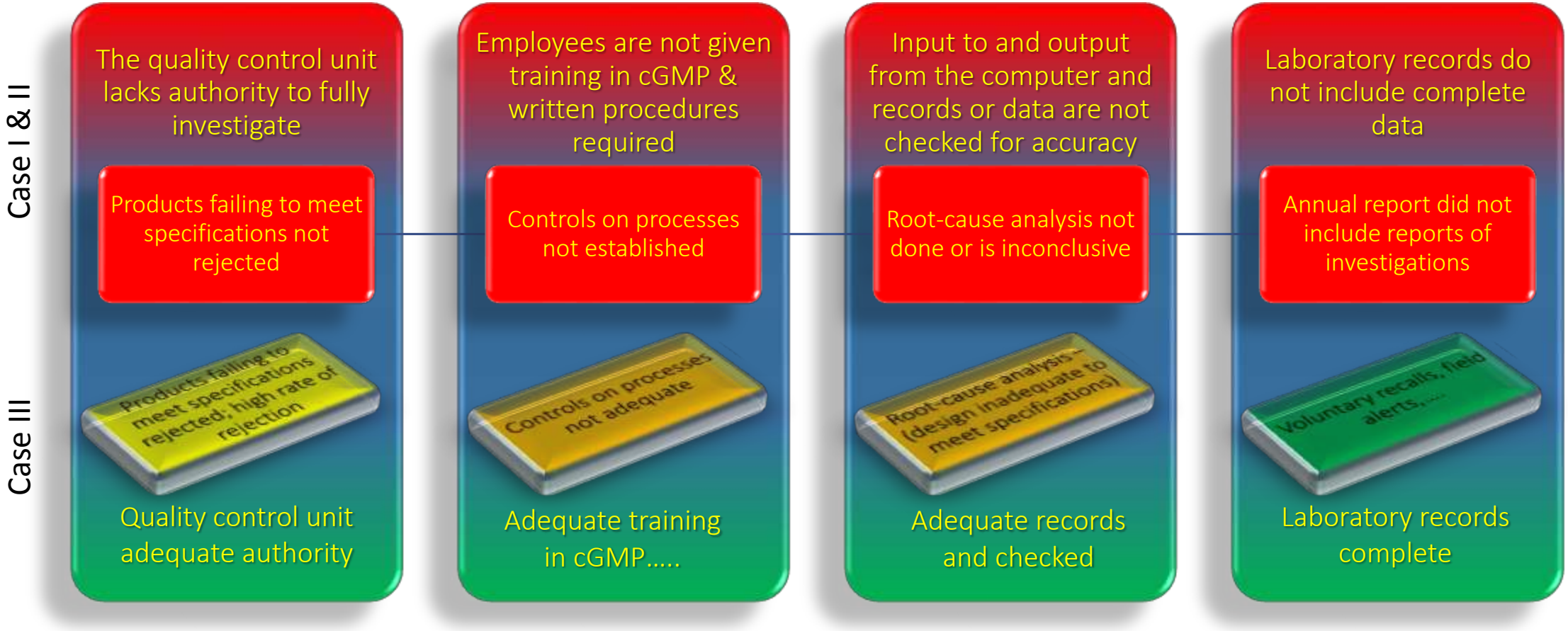
March 9, 2007: Four pleaded guilty - “duping the FDA for six years.”

Federal Register Vol. 77, No. 66, April 5, 2012 Notices : Debarment

Root-cause(s)?

Three case examples – from experience at FDA	**Case I** View point: Observer	"Conspiracy to commit an offense against the United States"	Bankruptcy and debarment of several individuals
	Case II View point: Expert witness for the prosecution	"Criminal prosecution"	Bankruptcy and…
	Case III View point: Arbitrator; to avoid drug shortage	Company complied with cGMPs for the product before a specification was changed (FDA/USP)	Had to re-develop their products to comply with cGMPs

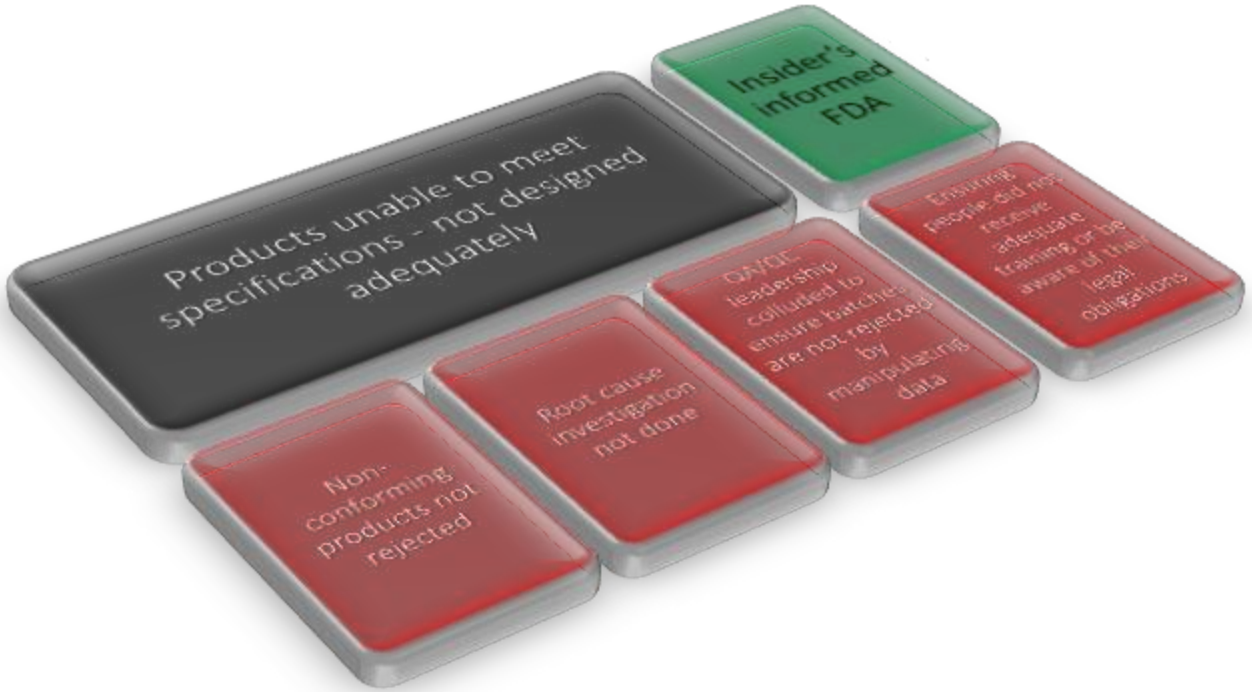
Case I & II vs. Case III



Case I: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/ucm061813.htm

What was the difference?

CASE I & II

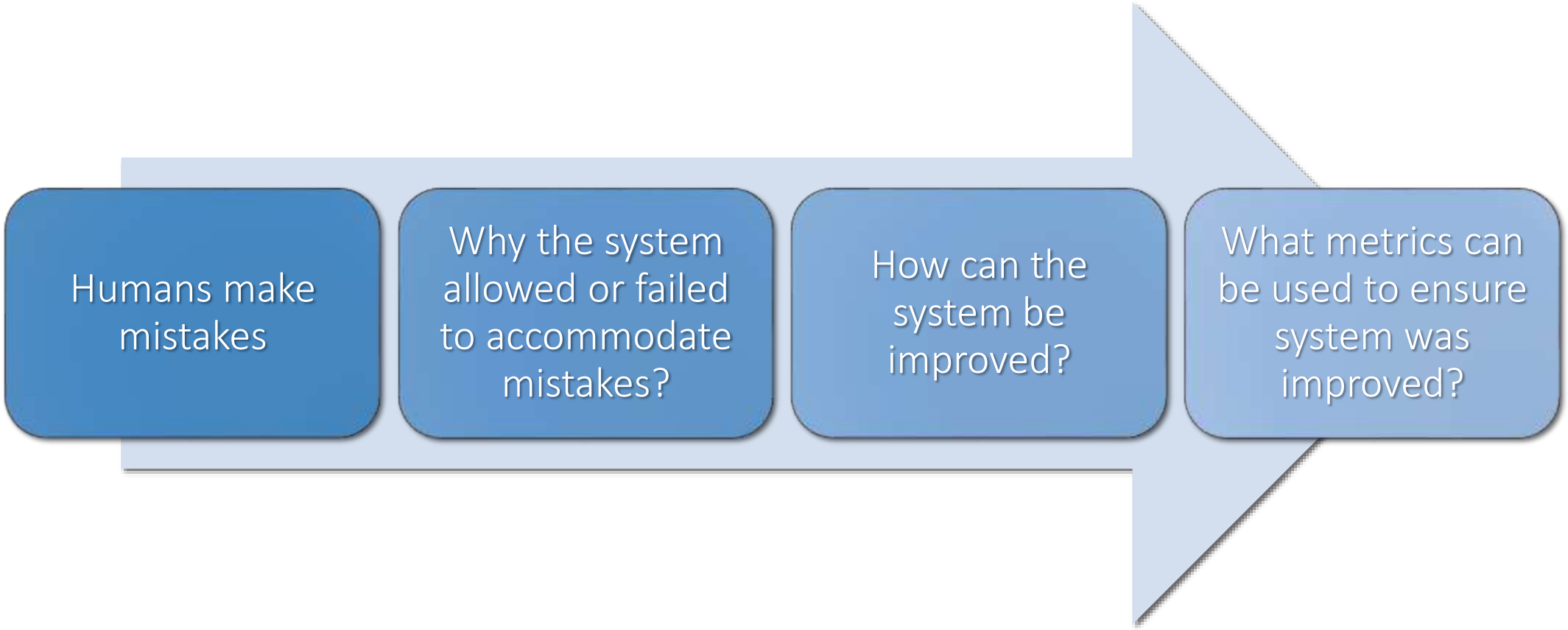


CASE III

Product unable to meet specification (following a change in specification – by FDA/USP)

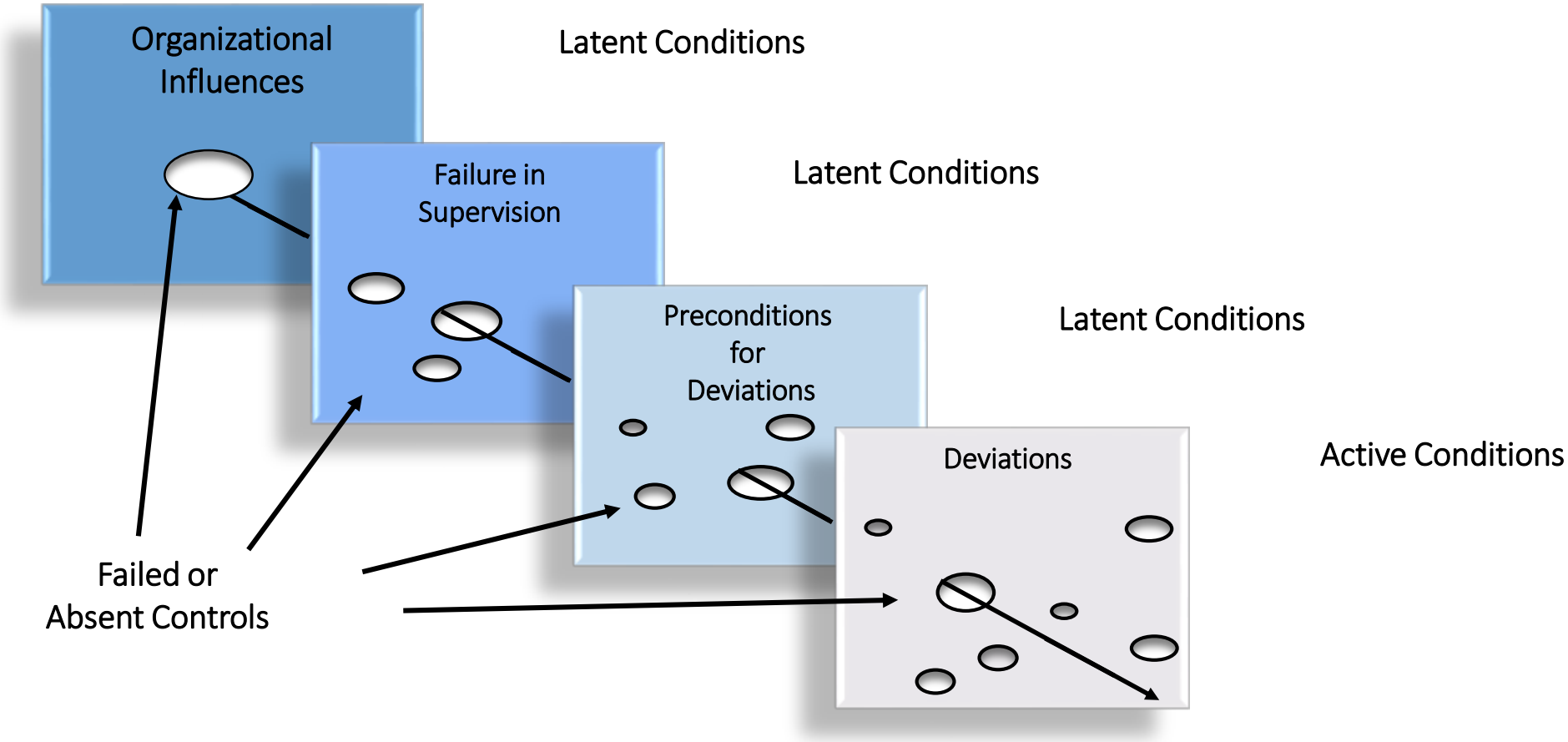
- Non-conforming product rejected and FDA notified
- Initial root cause investigation focused on (dissolution)test methods; product had to be redesigned to meet new specifications
- QA/QC adequate authority, people trained and supported to make decisions per legal requirements

Cognitive biases and errors

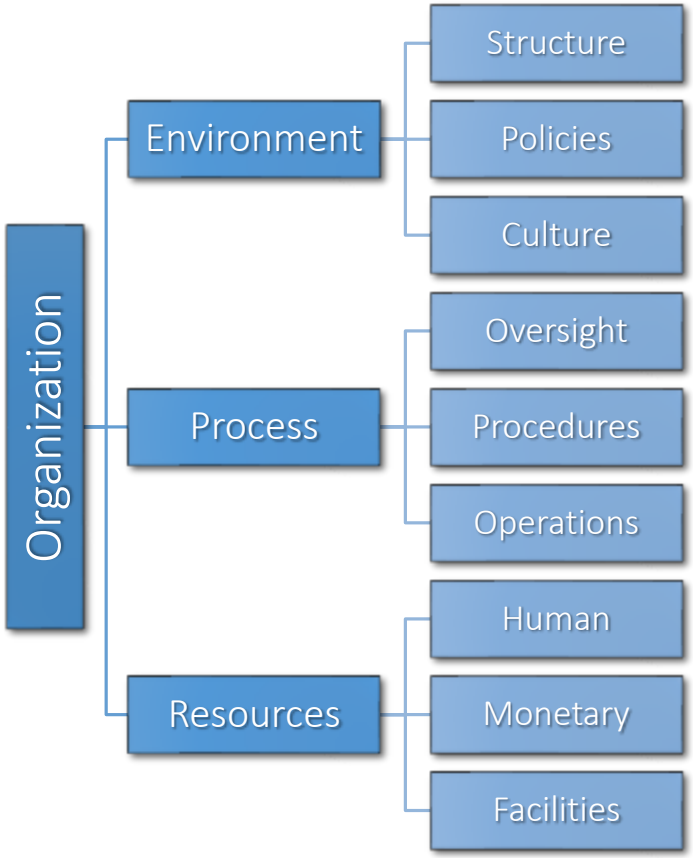


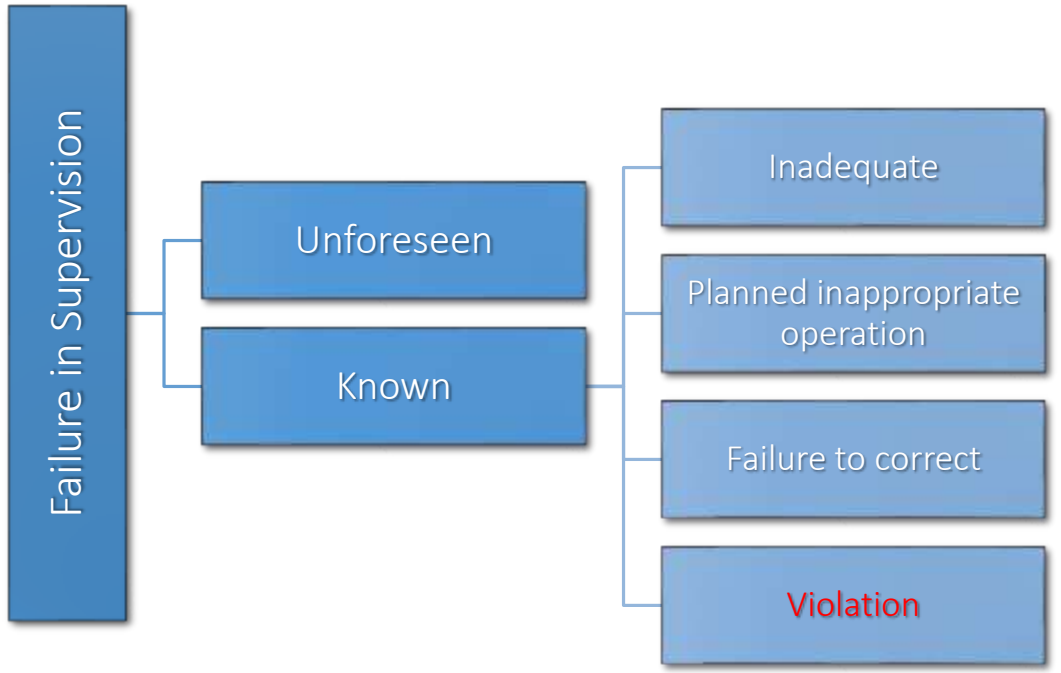
Human Factors Analysis and Classification System for CGMPs

Adapted from the Department of Defense Human Factors Analysis and Classification System

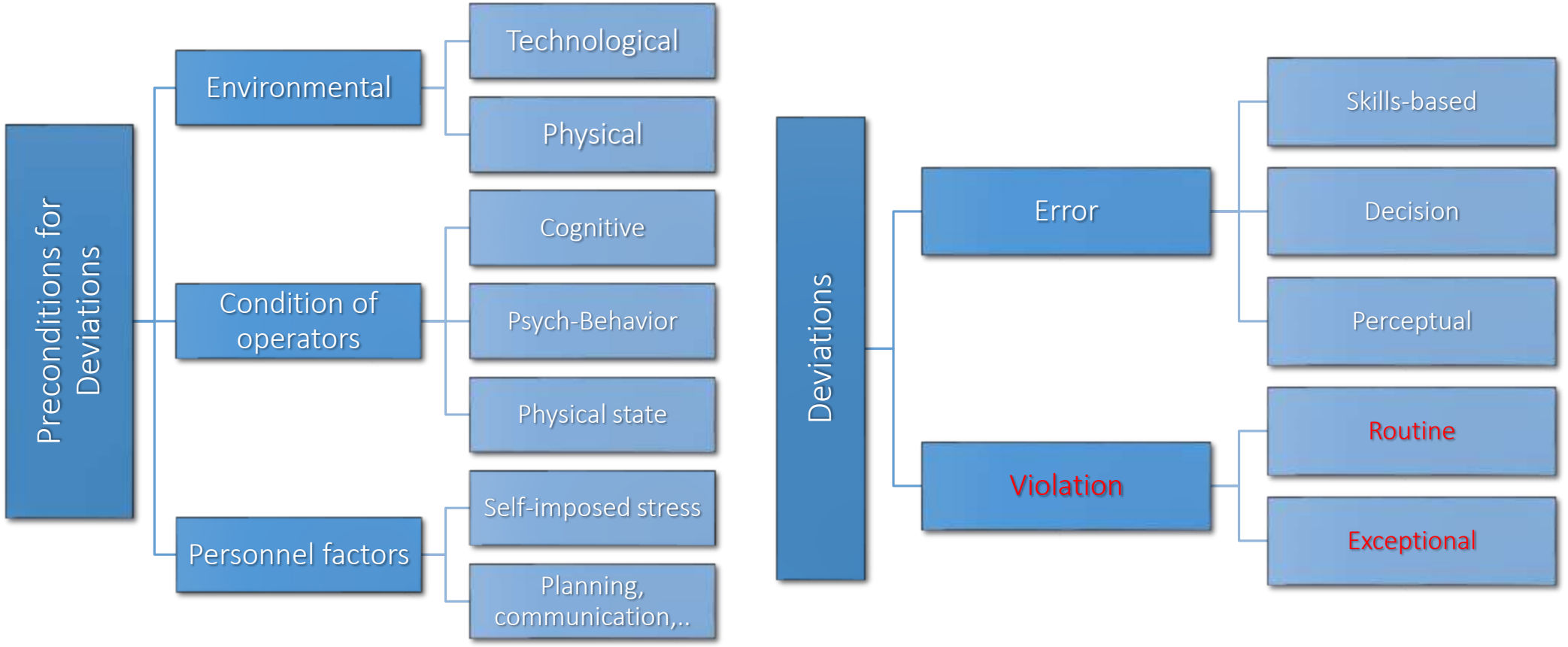


Organization & failure in supervision





Preconditions, deviations and violations

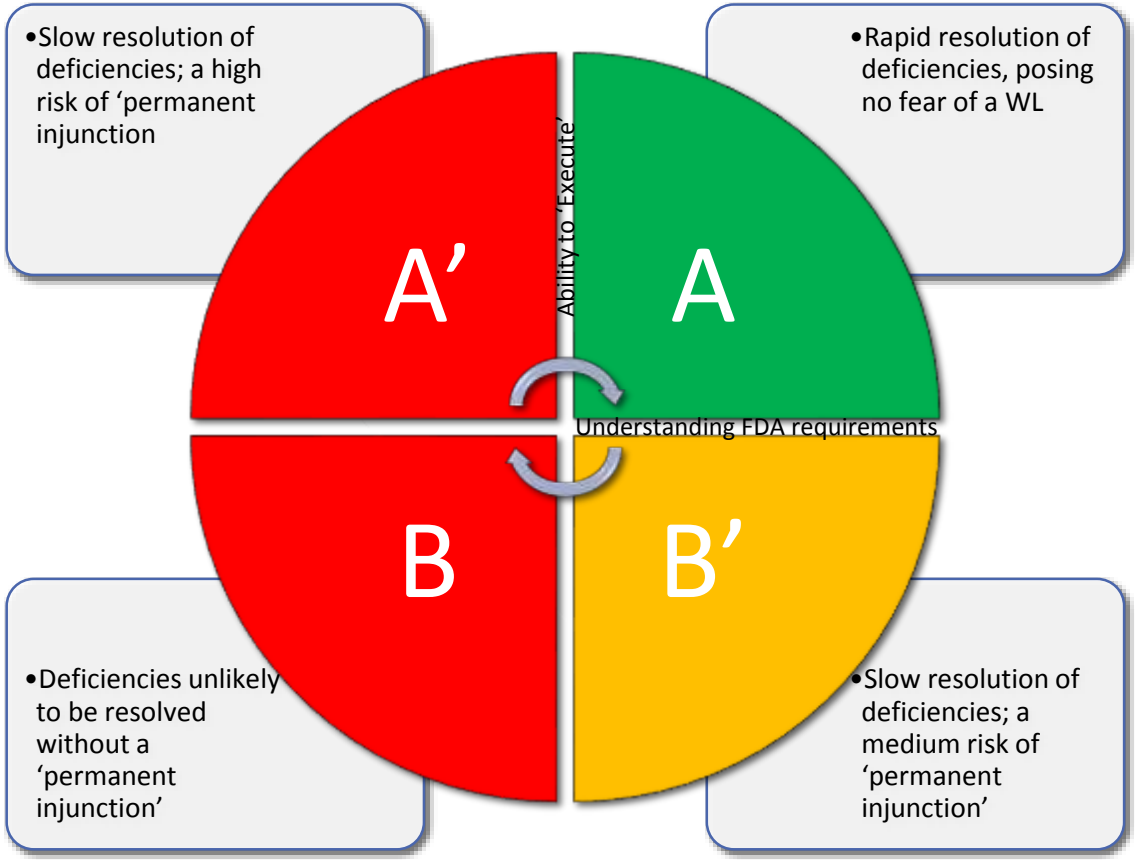


Reasons why firms should take time to learn from past issues

cGMP deficiencies observed frequently

- Established global companies, many based in the US & Europe, have not been immune
- Currently there are several on-going cGMP remediation programs; rate of resolution is highly variable
- FDA has rightly increased its inspection focus on foreign firms
- There are compelling reasons why these firms should take time to learn past issues

Self-resolution and no fear of a Warning Letter: Execute with understanding



A note about FDA…..

FDA is a unique organization

- There are setbacks, but it finds a way to improve continually
- Implementation of its 21st Century Initiative may have been slow; but it has changed the organization at its core

Quality of output

- Target of inspection and the quality of observation steadily improving – getting to the 'root cause'
- CMC review quality will improve further – a more logical question based review on the horizon

One particular area for improvement

- Understanding and controlling relevant variances during the development & review phase to set optimal specifications
- Effective knowledge sharing between CMC review and cGMP investigators

Changes at FDA CDER……

At FDA, focused attention on changes to ensure a more rational approach to CMC review and cGMP inspections

Understand and control sources of variances relevant to quality during development and review process

Improved understanding to make risk-based inspections

Rational question based review to ensure QbD; science based process validation,…

Improve ability to detect "too good to be true data and claims" (protracted detection and correction time)

Focus on prevention and reduce reliance on "whistle-blowers" and need for DOJ intervention? Additional 'quality metrics'.

Summary

Few companies have progressed in implementing QbD. Others, then, are at a (high) risk of cGMP issues as they have limited ability to conduct effective root cause investigations and hence effective CAPA.

Companies outside USA are particularly at a high risk of cGMP issues. FDA is rapidly expanding the rigor and frequency of their inspections. In the US, FDA inspections have generally been unannounced; facilities outside US have had the luxury of preparing for announced inspections. This is changing.

Ten years following the launch of the 21st Century Initiative the comment - "Generics are all about file first and figure out later" – should be disturbing to those who still remember the "generic drug scandal". Steps FDA is expected to take must ensure effective scientific development and validation.

Companies can and should take proactive steps to prevent catastrophic risks, improve predictability and create competitive advantage by utilizing the principles established under the 21st Century Initiative; a segment of the industry is already reaping benefits.

How well is your company prepared?

FDA organizational changes and focus on full implementation of the principles outlined in the FDA's Pharmaceutical Quality for the 21st Century initiative

Changes in generic drug review requirements, process and timelines

Full implementation of the FDA's process validation guidance

Focus on increased coverage and quality of foreign inspections