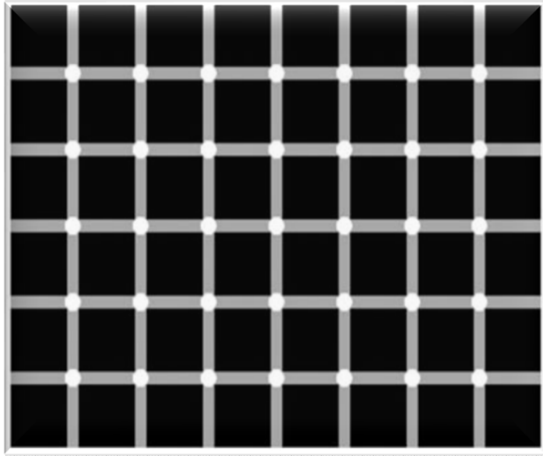
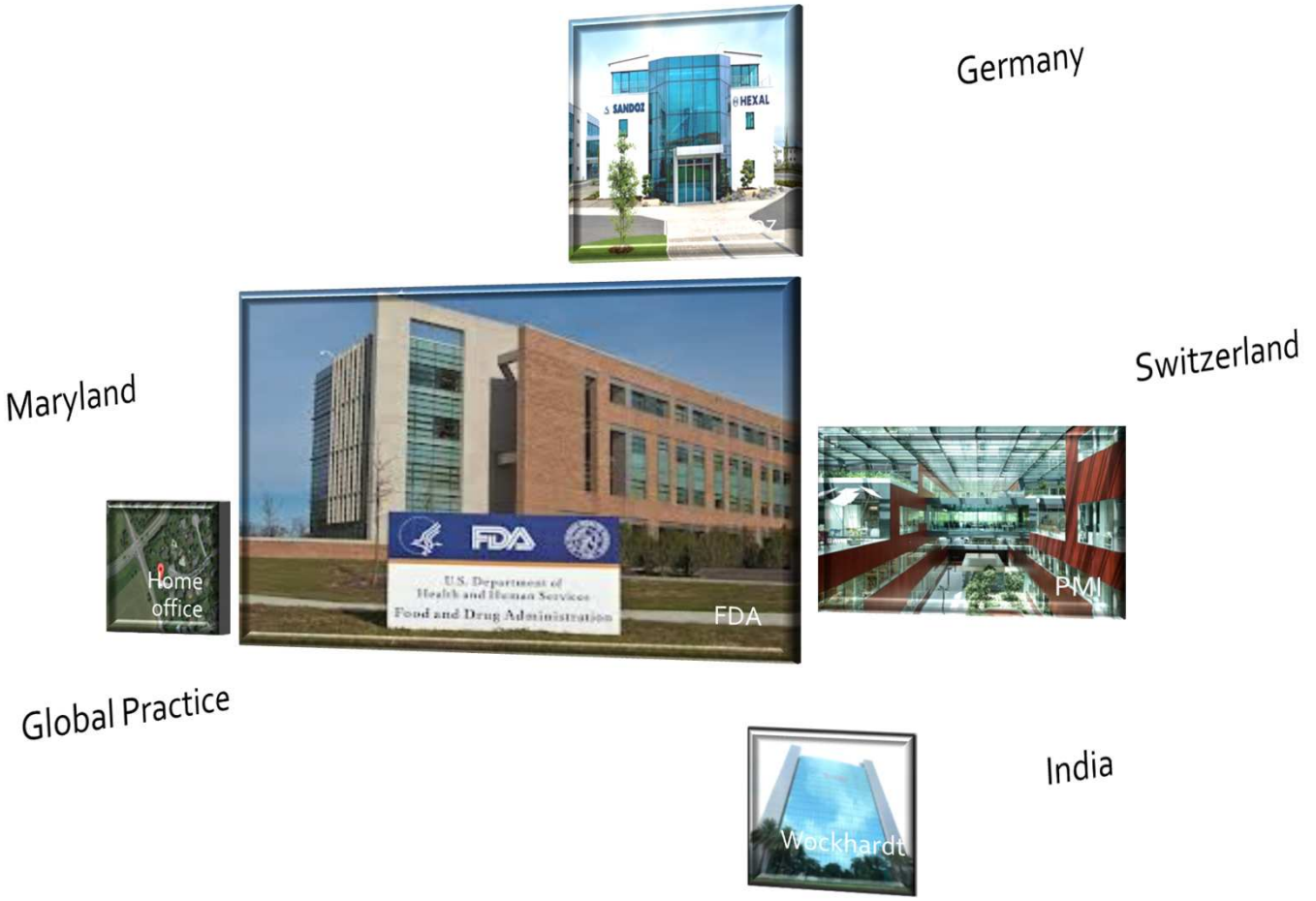
Reflections on PAT & QbD: 10 years

Ajaz S. Hussain, PhD

Insight, Advice & Solutions LLC



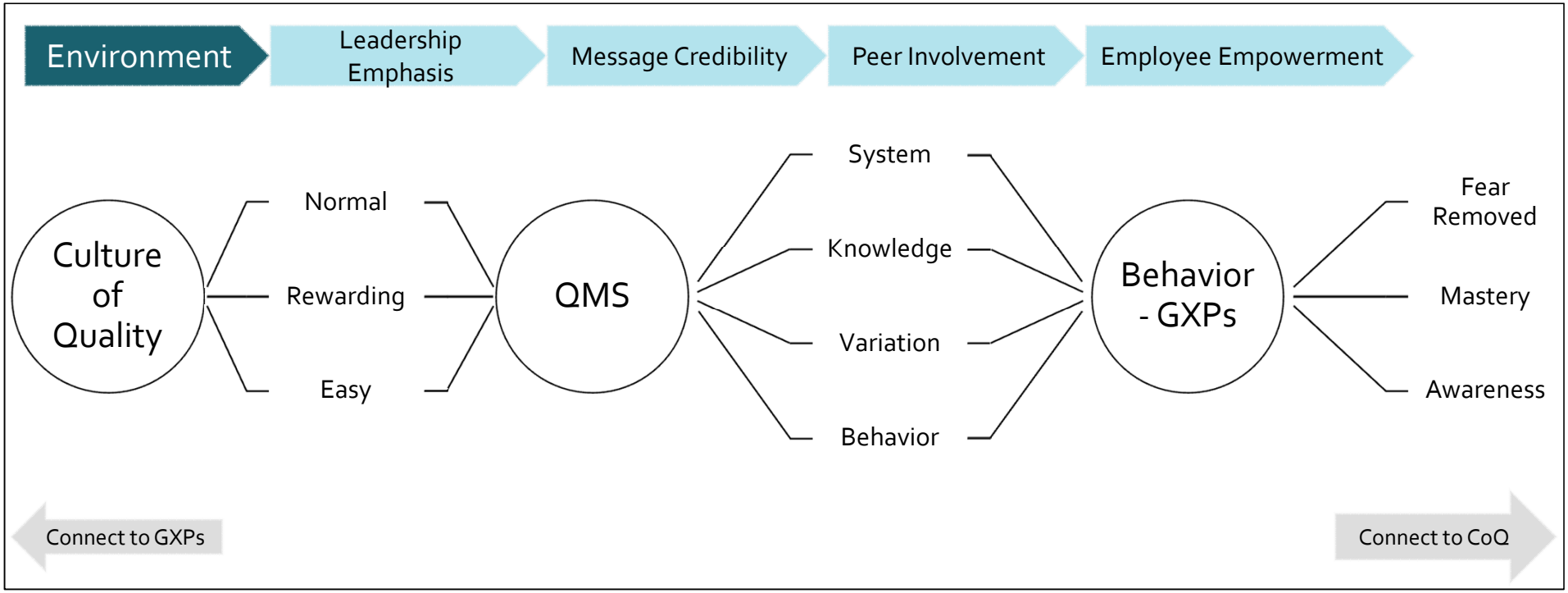
10 years since the first FDA report on the initiative Pharmaceutical Quality for the 21st Century.



Work to create a culture of quality (CoQ)

- Environment that facilitates individuals to guide their behavior to work consciously in the interest of patients and to continually improve this ability.

Integrated Framework: Culture of Quality

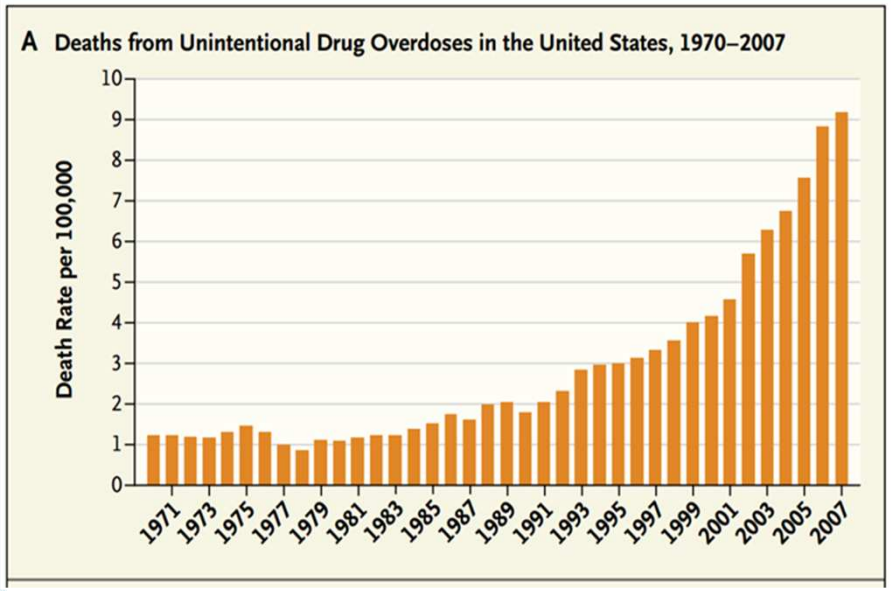


http://www.slideshare.net/a2zpharmsci/pharmaceutical-culture-of-quality

Human behavior

Why do we regulate?	Pharmaceuticals exhibit market failures that can have devastating consequences
What do we regulate?	Human behavior
How do we regulate?	Laws, regulations, policies, review, inspections, criminal prosecutions,…
Who are the regulators?	All of us, not just the FDA
What is the foundation for modern regulations?	Scientific evidence and compliance with regulations and 'Good Practices'

Reminder – we all are regulators



A Flood of Opioids, a Rising Tide of Deaths. Susan Okie. N Engl J Med (2010)

On PAT, QbD.....

- ".....significant, laid the groundwork,... but did not go to the logical end,...we are determined to .... now"
- I encourage you to review her speech ... click on the photograph..

FDA CDER Challenges & Changes: Today

FDA's Stern Warning On Data Integrity (The Pink Sheets, 21 July 2014)

If the agency's trust is lost it will be difficult to earn it back; posing challenges far beyond an initial manufacturing setback.

Complete honesty after a slip up will go a long way

Although India and China have been the current focus, FDA is seeing data integrity breaches everywhere to some degree.

The new (proposed) Office of Pharmaceutical Quality, CDER, FDA

One Quality Voice; Value Statements

<u>Put patients first</u> by balancing risk and availability

Have one quality voice by integrating review and inspection across product lifecycle

Other points; see: FDA/CDER's Office of Pharmaceutical Quality http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCMaug468.pdf

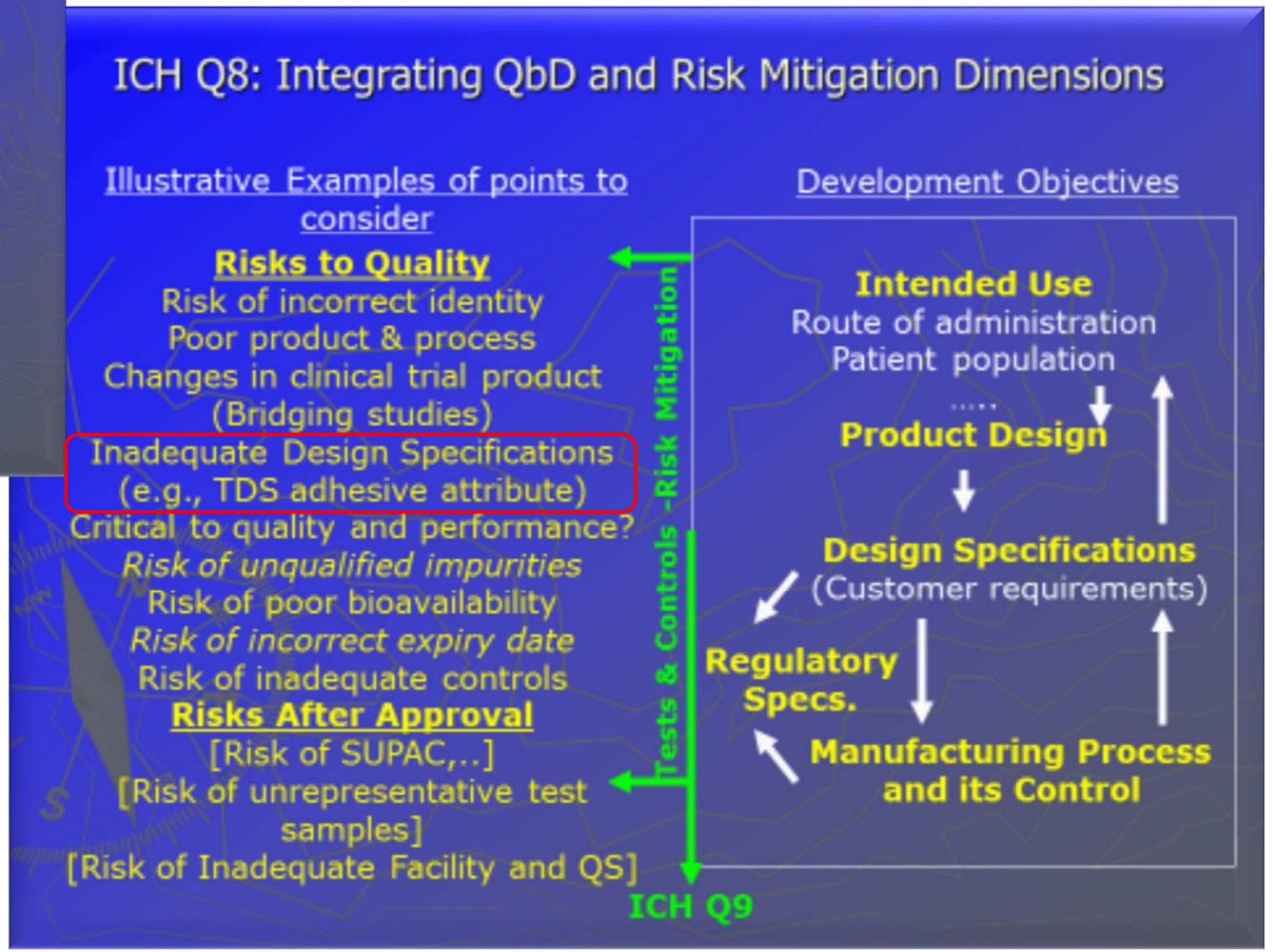
Continuous learning and improvement

- Regulating Fentanyl Transdermal Patches (a effective drug when used in the intended population and used properly)
  - Design and develop robust products – recognizing and addressing likely *failure modes*
  - Effective review and approval – asking the right questions
  - Prescription only for the intended patient population
  - Verify before dispensing and provide instructions to ensure understand how to use and dispose properly
  - Effective pharmacovigilence, corrections, learning and improvements

Challenges and Opportunities in Enhancement of the CMC Section of NDAs: Quality – by - Design

Ajaz S. Hussain, Ph.D.
Deputy Director
Office of Pharmaceutical Science
CDER, FDA

DIA Annual Meeting, Washington D.C., June 2004



Why adhesive performance is a critical quality attribute for all TDS?

Why was/is this not adequately recognized?

High incidence of deliberate abuse or suicide

Fatal Fentanyl Patch Misuse in a Hospitalized Patient with a Postmortem Increase in Fentanyl Blood Concentration.

- J Forensic Sci. 2014 Jul 17.

Notes from the field: increase in fentanyl-related overdose deaths - Rhode Island, November 2013-March 2014.

- MMWR Morb Mortal Wkly Rep. 2014 Jun 20;63(24):531

Opioid overdose mortality in Kansas, 2001-2011: toxicologic evaluation of intent.

- J Anal Toxicol. 2013 Nov-Dec;37(9):629-35.

Uninformed, improper use

Opioid overdose in a patient using a fentanyl patch during treatment with a warming blanket.

Anesth Analg. 2001 Sep;93(3):647-8

Life-threatening coma and full-thickness sunburn in a patient treated with transdermal fentanyl patches: a case report.

J Med Case Rep. 2012 Jul 26;6:220.

High residual drug; disposed improperly

Poor adhesive performance; accidental patch transfer

Fentanyl Patch Can Be Deadly to Children

FDA has issued two public health advisories—in 2005 and 2007—about the safe use of fentanyl patches and today it is continuing its outreach to patients, caregivers and health care professionals about the dangers of accidental exposure.

http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm300803.htm

Recalling an investigation of a case that strongly suggested adhesive failure can lead to patient frustration and can pose risk of repeated patch replacements (reservoir effect?); report presented to CDER Drug Safety Oversight Board (July 2005)

ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics

Volume 64, Issue 1, August 2006, Pages 1–8

Review article

Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute

Anna M. Wokovich[a], Suneela Prodduturi[a], William H. Doub[a], Ajaz S. Hussain[b], Lucinda F. Buhse[a]

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Received 10 January 2006, Revised 17 March 2006, Accepted 31 March 2006, Available online 15 April 2006

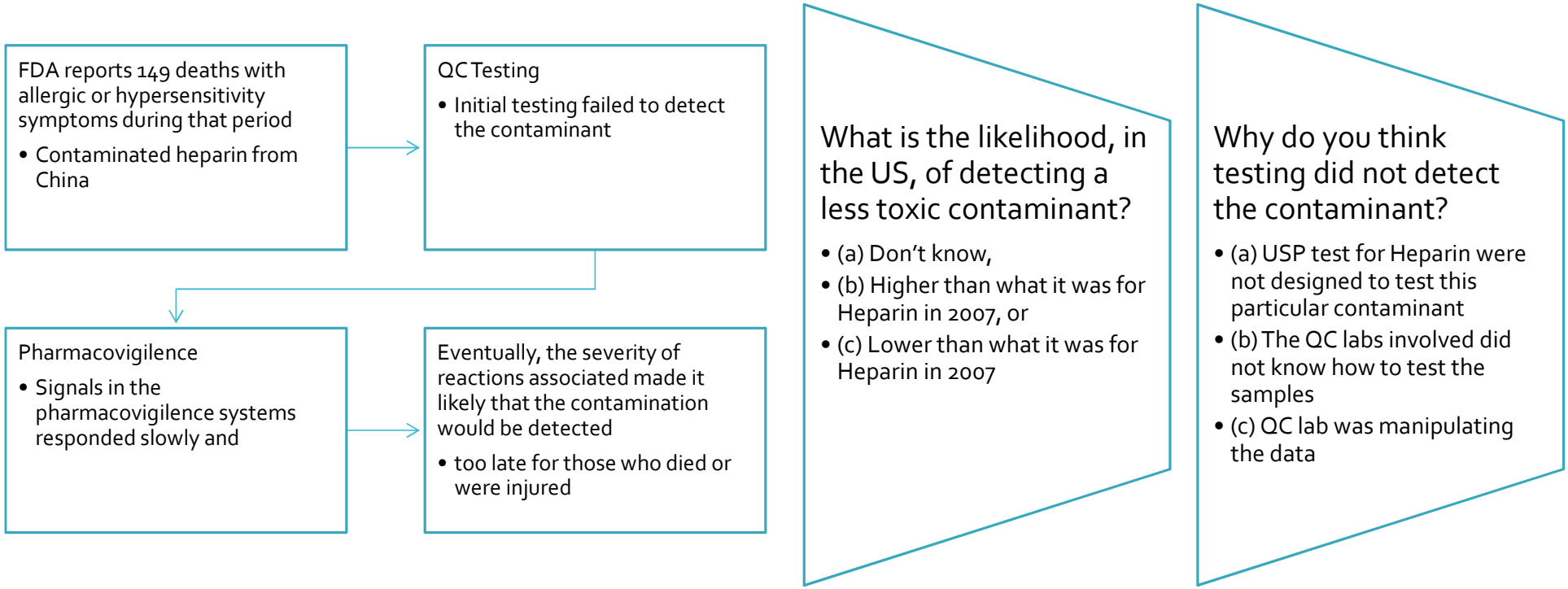
July 15, 2005 FDA Public Health Advisory: Safety Warnings Regarding Use of Fentanyl Transdermal (Skin) Patches

- Alert for Healthcare Professionals
  - FDA recently conducted a review of fatalities reported to the voluntary adverse event reporting system that were possibly due to unintentional overdose from the fentanyl transdermal patch
  - In many cases, establishing whether the overdose was unintentional was difficult
- Factors identified as possibly related to unintentional overdose included:
  - Use of high doses of the fentanyl patch and/or multiple patches (sometimes in combination with other drugs),
  - Possible medication errors, accidental exposure (e.g., coming in contact with a discarded patch),
  - Application of a heat source to the patch possibly resulting in increased fentanyl absorption,
  - Suspected transdermal patch malfunction (e.g., leaking patches).
  - In addition, several patients reported poor adhesion of the patches to the skin.

What is the current state?

- Adhesive properties: a critical issue in transdermal patch development. Expert Opinion on Drug Delivery. January 2012, Vol. 9, No. 1 , Pages 33-45
- "*numerous reports of in vivo 'adhesion lacking' are still addressed to regulatory agencies*"
- ***"Expert opinion:*** *The Pharmacopoeias should consider the opportunity of introducing compendial testing to assay the quality of adhesive patch properties, and regulatory agencies should issue proper guidelines to evaluate these features during development.*"

The US Heparin Tragedy 2007 and 2008



THE HEPARIN DISASTER: CHINESE COUNTERFEITS AND AMERICAN FAILURES
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS OF THE COMMITTEE ON ENERGY AND COMMERCE
HOUSE OF REPRESENTATIVES. ONE HUNDRED TENTH CONGRESS SECOND SESSION. APRIL 29, 2008. Serial No. 110-109

Mr. Shimkus: *When the drug safety system fails, people get sick. Some die.*

It is hard to detect harm	• *Some of these people are already very vulnerable, and proving the cause of harm from impurities, adulteration, and counterfeits can be elusive.*
FDA inspectors look for a culture of quality at manufacturing facilities.	• *Certainly the companies are obligated to ensure a culture of quality and maintain vigilance as well. This reflects a systems approach to safety.*
This system approach wasn't at play here.	• *FDA policies led to the failure to inspect the Chinese plant.*
This brings me to China and its quality culture or lack thereof.	• *While it doesn't deny the counterfeit source, tries to say that counterfeits didn't cause the reaction, as if the adulteration itself was no big deal. Is this an acceptable mindset? .....*

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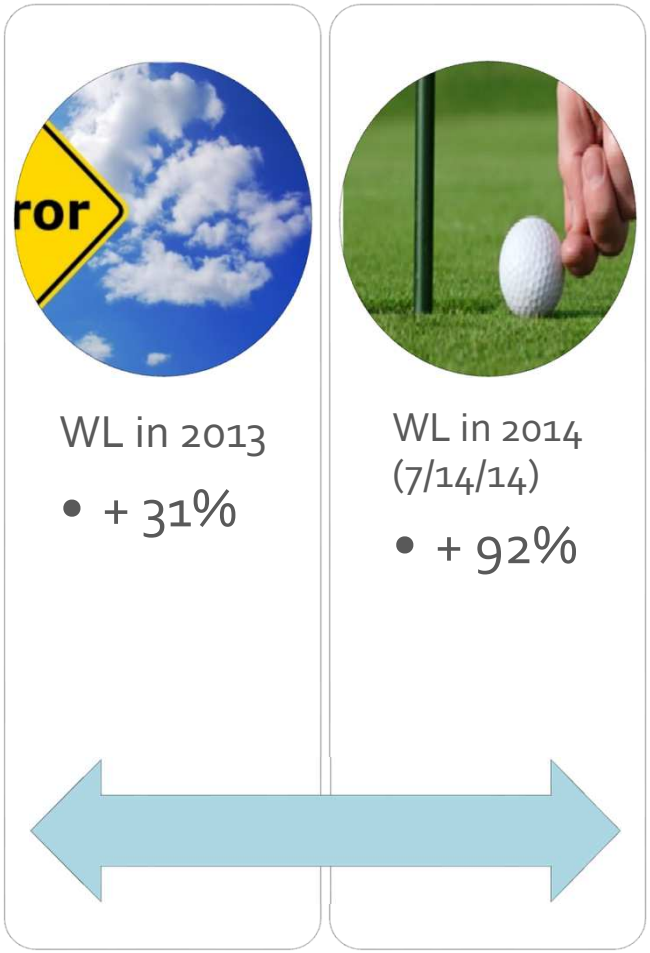
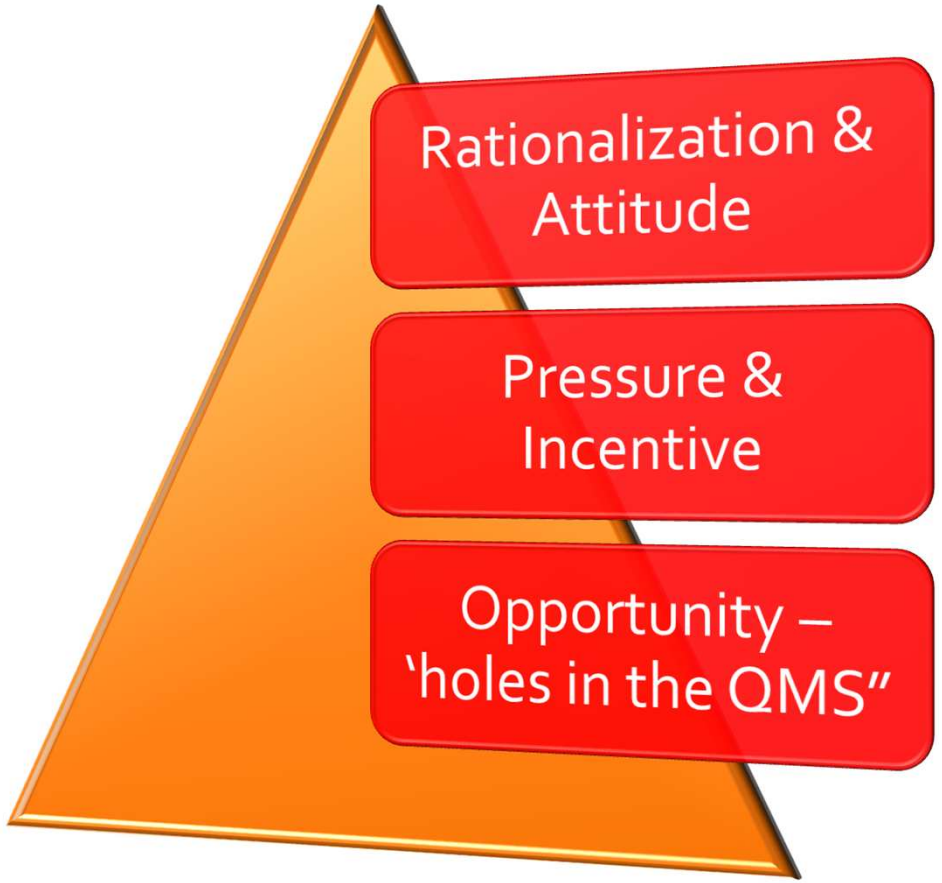
92% of Warning Letters in 2014 (until 7/14/14) related to lapses in data integrity

- Not recording activities contemporaneously
- Backdating
- Fabricating data
- Copying existing data as new data
- Re-running samples
- Discarding data

Alicia M. Mozzachio, RPh, MPH, July 15, 2014; FDLI, Washington, DC.



Preconditions to malice or disregard



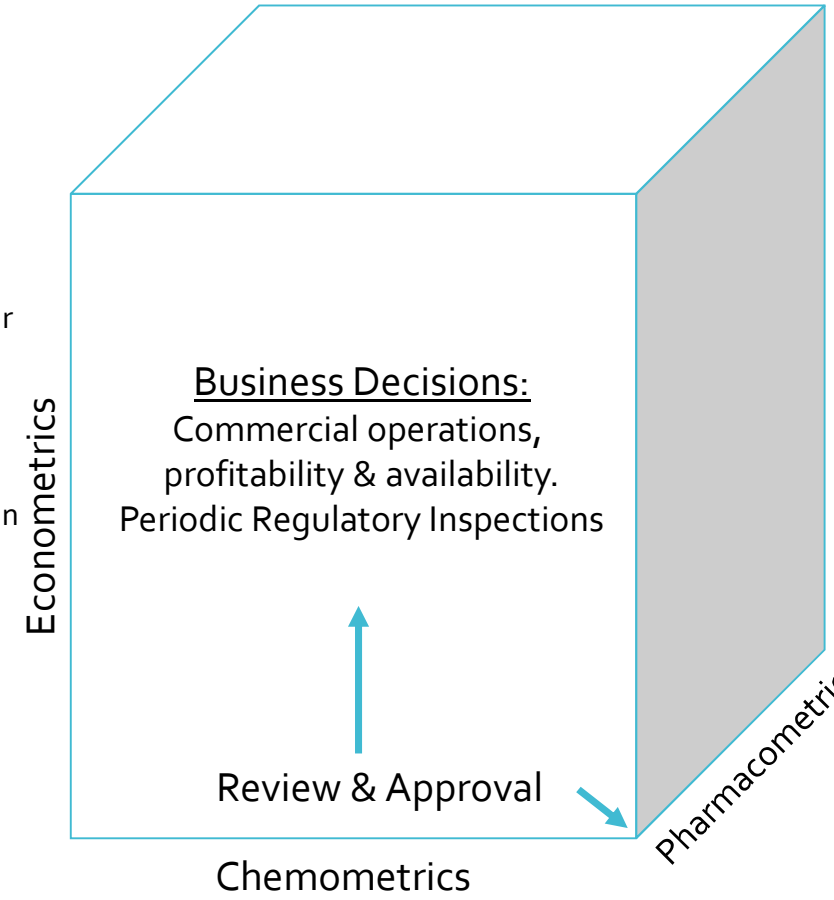
Chemometric, Pharmacometrics & Econometrics: Three Dimensions of QbD. Ajaz S. Hussain. Swiss Pharma (2012).

How do people really make decisions?

Prospect Theory: An Analysis of Decision under Risk. Daniel Kahneman and Amos Tversky Econometrica. 47: 263-291 (1979)

The Framing of Decisions and the Psychology of Choice. Amos Tversky and Daniel Kahneman Science. 211, pp. 453-458 (1981)

The End of Rational Economics. Dan Ariely. Harvard Business Review, July 2009.

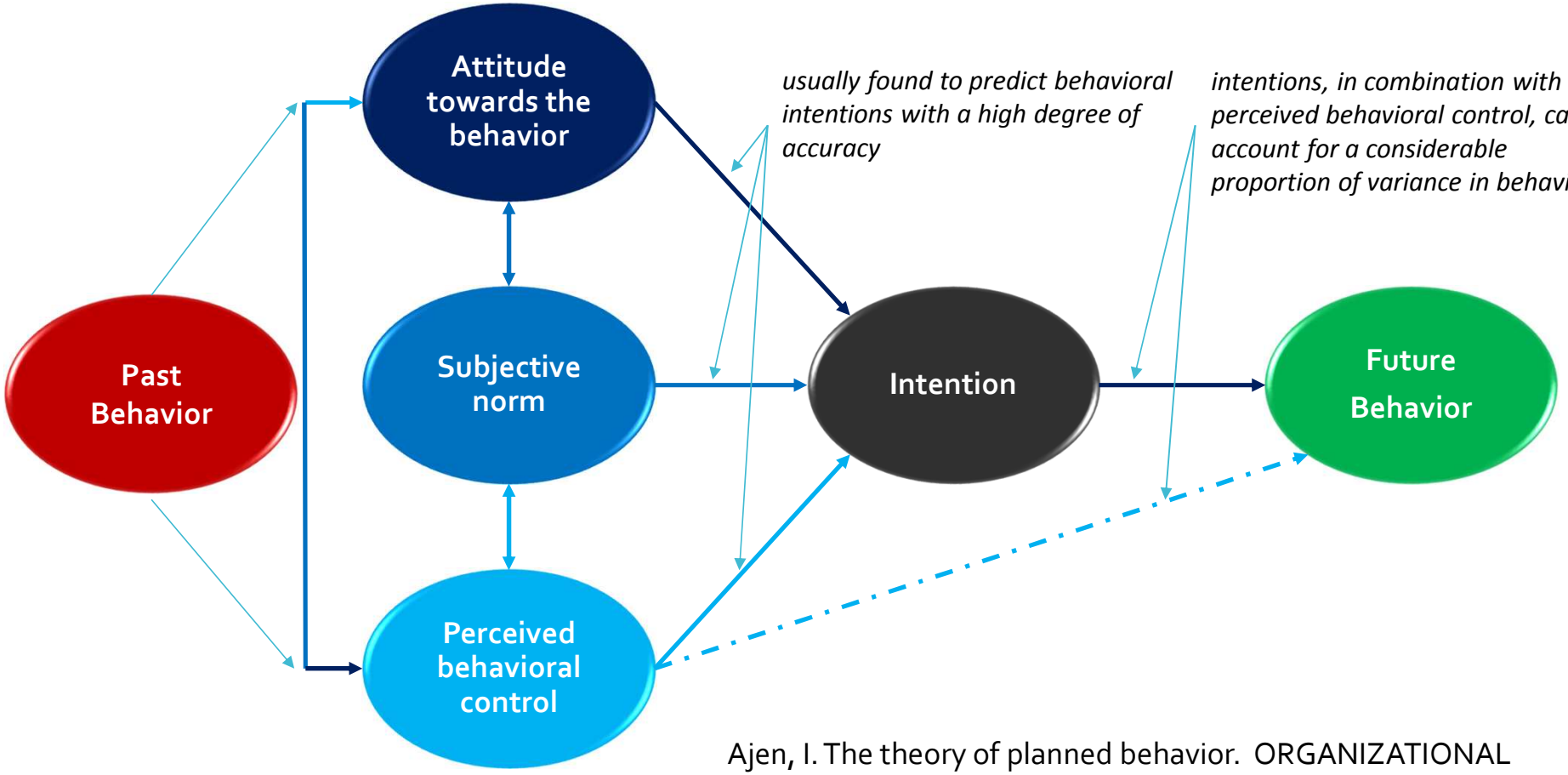


Three Econometric Papers on Quality

Decay, Shock, and Renewal: Operational Routines and Process Entropy in the Pharmaceutical Industry. Gopesh Anand, John Gray, and Enno Siemsen. Organization Science. 23:1700-1716 (2012)

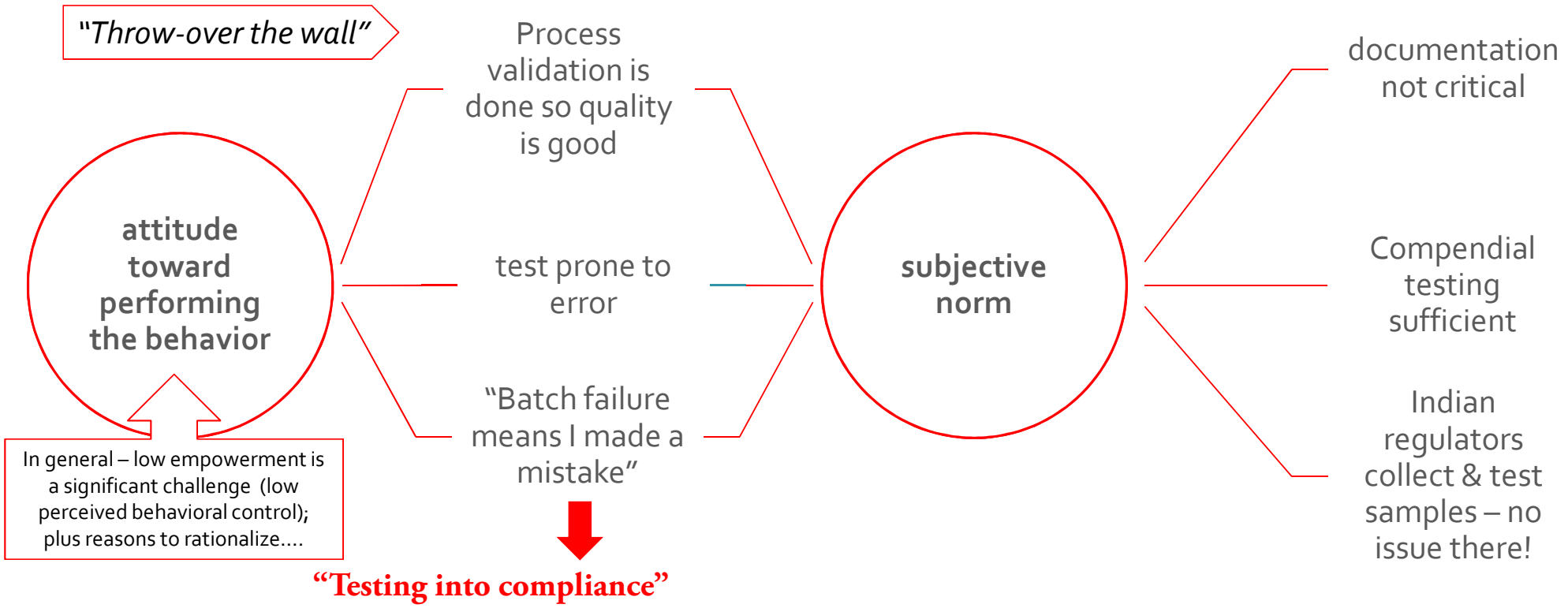
Regulator Heterogeneity and Endogenous Efforts to Close the Information Asymmetry Gap: Evidence from FDA regulation. Jeffrey T. Macher, John W. Mayo and Jack A. Nickerson. Journal of Law and Economics. 54: 25 – 54 (2011)

Quality Risk in Offshore Manufacturing: Evidence from the Pharmaceutical Industry. John Gray, Aleda Roth, and Michael Leiblein. Journal of Operations Management. 29: 737–752 (2011)



Ajen, I. The theory of planned behavior. ORGANIZATIONAL BEHAVIOR AND HUMAN DECISION PROCESSES 50, 179-211 (1991)

At the individual level, in QC function– how often does this occur?



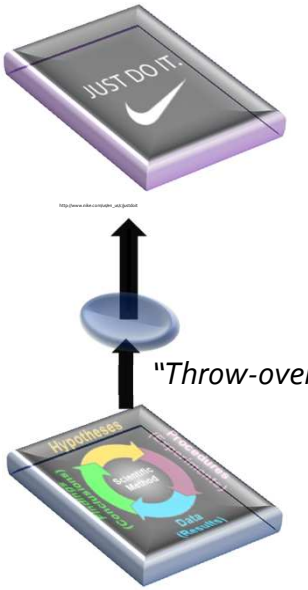
Root-cause may be upstream!

Satisfy reviewer requirements

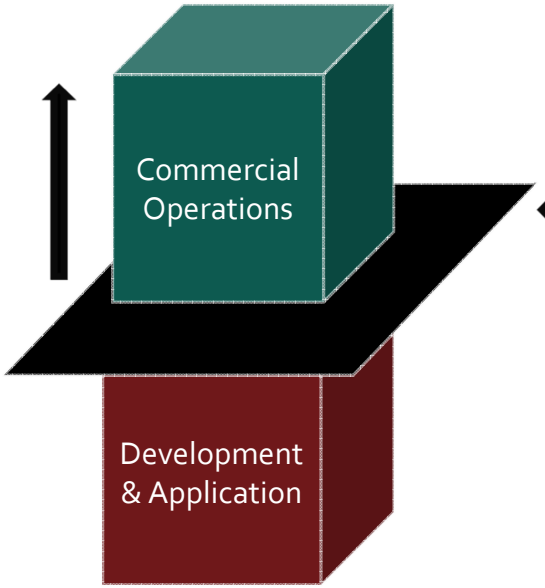
Throw-over the wall

Then just do it …

Prone to 'process entropy' without FDA Inspections!



"Throw-over the wall"



Pharmacovigilance Inspections – 483, WL,…
Marketing,….
Manufacturing

<u>Marketing Authorization</u>

Pre-Approval Inspection
Review
Application
Development

"Satisfy Reviewer Requirements"

CoQ Manifests in the Organization's Environment by Design

Different functions connected directly or indirectly to the two products (medicine and evidence) – their outputs impacts quality of these products

- Each function within its environment should be working to ensure the two products are consistently linked [directly or via the chain of evidence to the clinical trial product that established the pivotal evidence of benefit and risk that allows the product to be sold]
- Multitude of individuals from various disciplines of science, engineering, management .. Each expected to be disciplined within their disciplinary methodologies; a proportion of staff may not have formal training in any disciplinary methodology

The phrase by design in Quality by Design – is therefore, a foundation of CoQ.

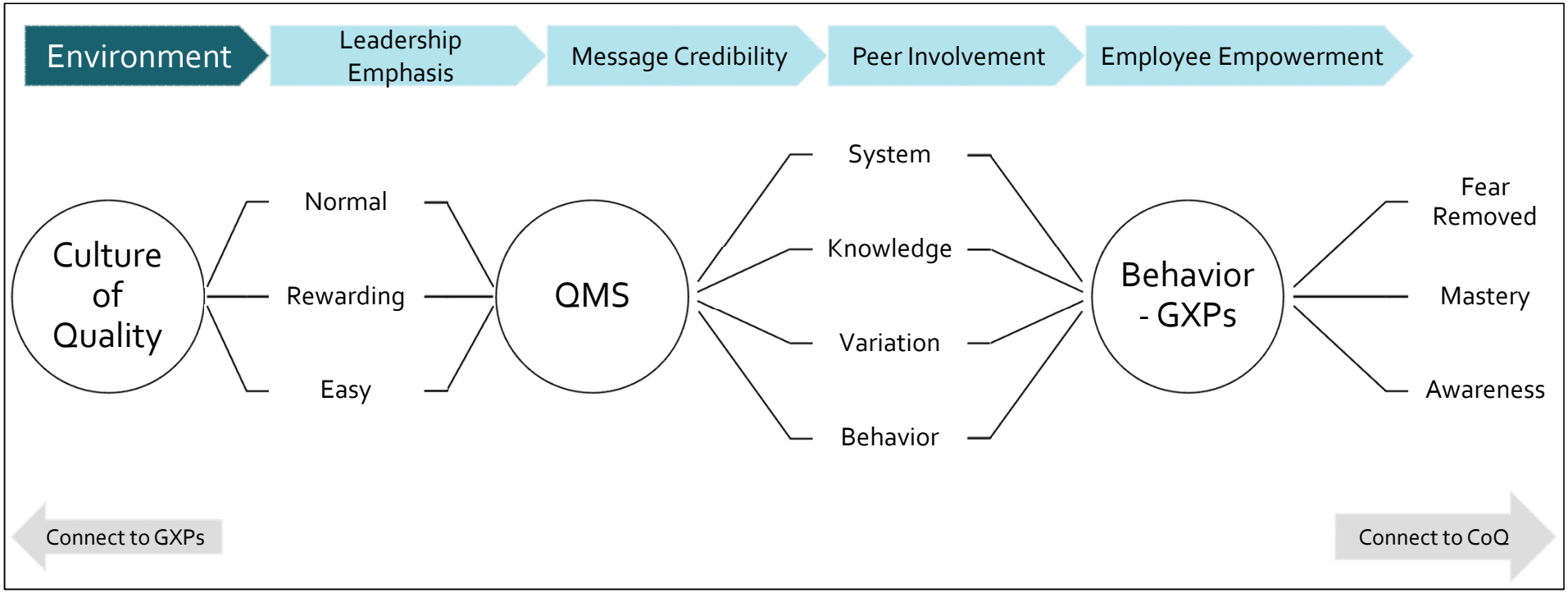
- In this course CoQ – QMS- GXP and QbD – are viewed and discussed in the most basic elements – intention and behavior
- "Features of Quality by Design: Doing things consciously"

Consciously ask the right questions in the interest of the patients, describe the accepted assumptions and set the level of precision needed for the answers to the questions posed. Be a good scientist – in the interest of the patients.

Consciously	• Scientific methodology • Engineering Design • Plan-Do-Check-Act
Subconsciously	• Habits (work to get rid of bad ones) • Habits (work to cultivate good one) • Keystone habits (Safety @ Alcoa; A.L.C.O.A. of data integrity)

The Power of Habit: Why We Do What We Do in Life and Business. Charles Duhigg (2012)

Integrated Framework: Culture of Quality



http://www.slideshare.net/a2zpharmsci/pharmaceutical-culture-of-quality

Culture of Quality

We do our best to develop medicines and the evidence to meet the needs of patients – we develop these products consciously recognizing quality cannot be tested into our products .

We recognize that nothing is perfect and there will be some errors in our design, systems and procedures, or we may make mistakes in following set procedures.

It is normal, easy and rewarding to work within our quality management system, without fear, to detect, correct and to learn from our mistakes.

In doing so we act consciously in the interest of patients – specially when no one is looking, and continually improve our quality by design and aim for right first time.