



Key Trends In Quality and GMP Inspections

Indian Pharmaceutical Alliance pharmaceutical workshop

November 12 – 20, 2018

Goa, Hyderabad & Ahmedabad, India

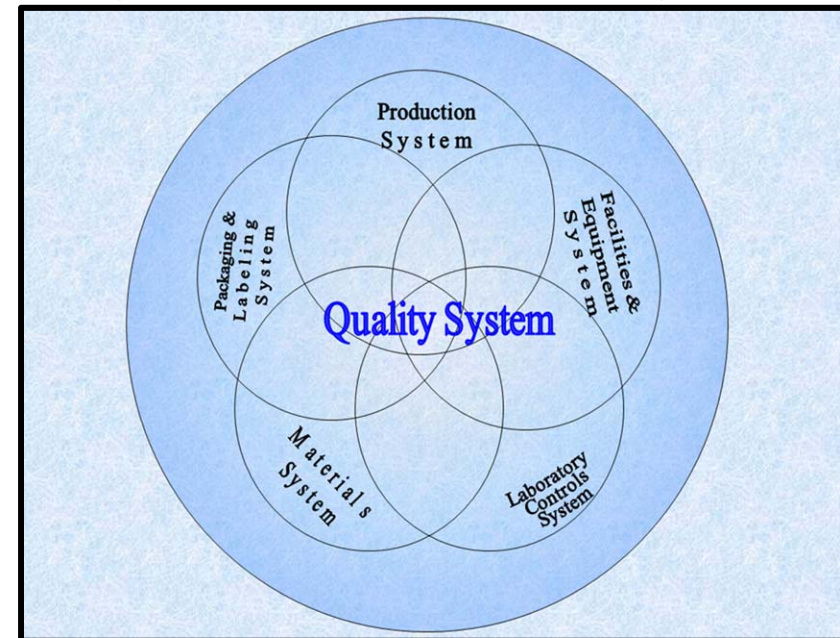
Quality

All pharmaceutical inspections include a verification of a company's compliance with regulations and CGMPs;

Which will include an assessment of the Quality Unit e.g.,

- the capabilities of the Quality oversight program;
- an assessment of effectiveness of the Quality Unit; and,
- if there are CGMP gaps, are they chronic or sporadic?
- are the CGMP gaps corrected?

Quality starts at the top but it is everyone's responsibility.
All systems are interrelated with the Quality System.



Quality Control Unit (QCU) Definition

21 CFR 210.3(b)(15)

- Quality control unit means any person or organizational element designated by firm to be responsible for the duties relating to quality control.

The QCU is typically divided into Quality Assurance and Quality Control (Laboratory) units.

Note – the term Quality Control is commonly used in reference to the laboratory. The term used in the CFR is in reference to the organizational unit (e.g., Quality Assurance) that is responsible for the overall Quality of the manufacturing and QC testing.

Quality Control Unit

- EVERY firm, regardless of size, **must** have a Quality Control Unit. The preamble to the CGMP regulations published in 1978 states:

“This means that in very small operations a single individual can function as the quality control unit.

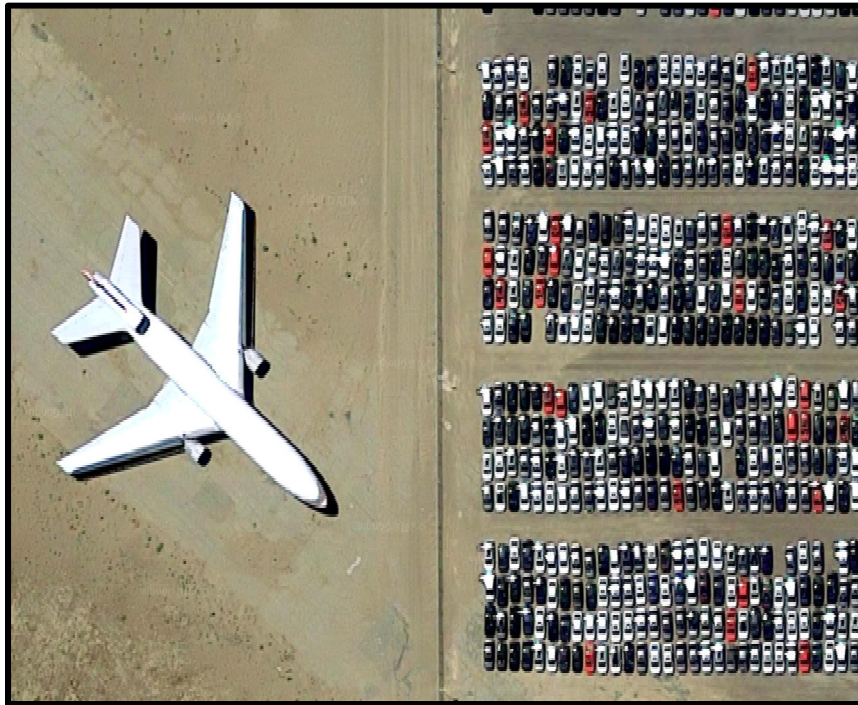
But that person has the responsibility for implementing all the controls and reviewing the results of manufacturing to assure that drug product quality standards have been met.”

Quality System Coverage

- Evaluate whether the Quality Unit has met its responsibility, for example, to;
 - review and approve all procedures related to production,
 - quality control, and quality assurance,
 - and assure the procedures are adequate for their intended use,
 - including the associated recordkeeping systems.

- Assessment of the supporting documentation and quality data collected by the Quality Unit.

Imagine the Quality Unit



As an example –

- Let's imagine an auto parking lot with new automobiles that have been recalled; and,
- Your department was the Quality Unit that approved and released the autos for sale;
- What do you do now?

Imagine the Quality Unit

- As an example - How many VW autos do you think are in this California, USA lot?
- nearly 300,000 VW diesels are sitting in lots across the U.S.



- Fox News March 30, 2018

Which comes to mind...

- “All of our social problems arise out of
 - doing the wrong thing righter.
 - The more efficient you are at doing the wrong thing,
 - the wronger you become.
 - It is much better to do the right thing wronger
 - than the wrong thing righter!”

- “If you do the right thing wrong and correct it, you get better!”

Management of f-Laws
How organization really work
2007, Russell Ackoff, Ph.D.

New York Times

November 25, 2015 – Business

Illustration by Guilbert Gates | Source: Volkswagen, The International Council on Clean Transportation

How Volkswagen Got Away With Diesel Deception

By KARL RUSSELL, GUILBERT GATES, JOSH KELLER and DEREK WATKINS UPDATED November 20, 2015

Volkswagen has admitted that millions of its diesel cars worldwide were equipped with software that was used to cheat on emissions tests. The company is now grappling with the fallout.

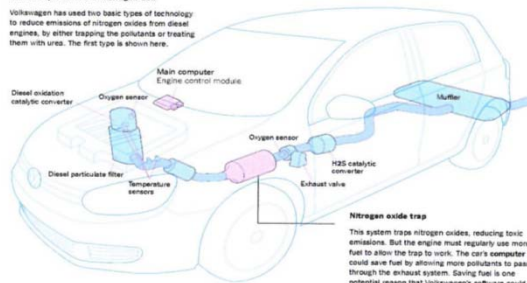
How Did the System Work?

The software sensed when the car was being tested and then activated equipment that reduced emissions, United States officials said. But the software turned the equipment off during regular driving, increasing emissions far above legal limits, possibly to save fuel or to improve the car's torque and acceleration.

It is not yet known which systems were modified. But experts are focusing on parts of the exhaust system that are designed to reduce emissions of nitrogen oxide, a pollutant that can cause

Exhaust system of a Volkswagen Golf

Volkswagen has used two basic types of technology to reduce emissions of nitrogen oxides from diesel engines, by either trapping the pollutants or treating them with urea. The first type is shown here.

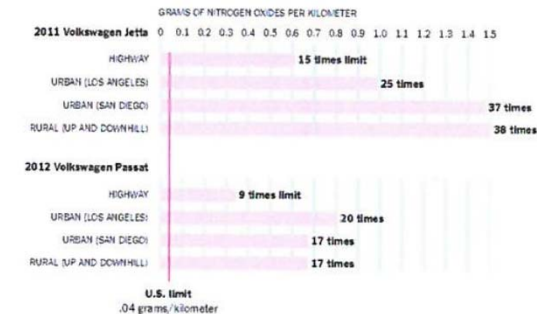


This system traps nitrogen oxides, reducing toxic emissions. But the engine must regularly use more fuel to allow the trap to work. The car's computer could save fuel by allowing more pollutants to pass through the exhaust system. Saving fuel is one potential reason that Volkswagen's software could have been altered to make cars pollute more, according to researchers at the International Council on Clean Transportation.

The Emissions Tests That Led to Discovery of VW's Cheating

The on-road testing in May 2014 that led the California Air Resources Board to investigate Volkswagen was conducted by researchers at West Virginia University. They tested emissions from two VW models equipped with the 2-liter turbocharged 4-cylinder diesel engine. The researchers found that when tested on the road some cars emitted almost 40 times the permitted levels of nitrogen oxides.

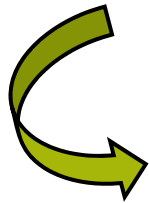
Average emissions of nitrogen oxides in on-road testing



Source: Arvind Thiruvengadam, Center for Alternative Fuels, Engines and Emissions at West Virginia University

Quality – is there a case for business

■ As an example:



- Volkswagen to Pay \$14.7 Billion to Settle Diesel Claims in U.S.

June 27, 2016 - New York Times

- Volkswagen Agrees to \$1.2 Billion German Fine in Emissions
-Cheating Scheme

June 13, 2018- European News

As a point of reference

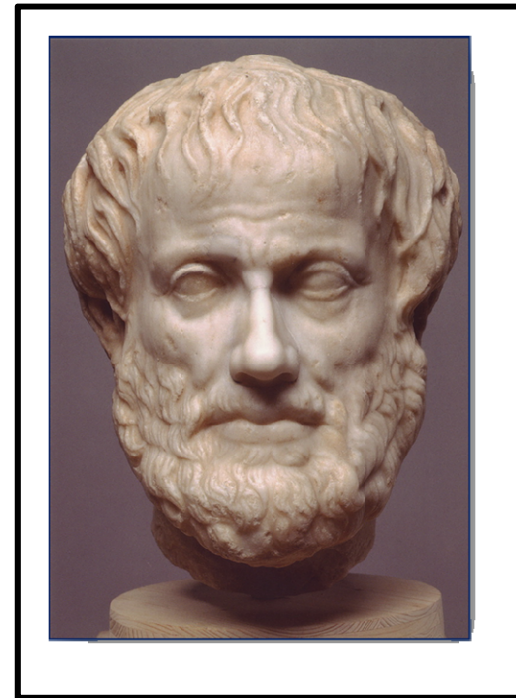


- April 1991 - A highly respected FDA Investigator mentioned; we (FDA) inspect about 5% of manufacturing operations during routine inspections
- So then, what is the 95% that we (FDA) don't see that's below the water line?
- A kind note to share, no one, absolutely no one, is more knowledgeable about your manufacturing operations and QC testing than you!
- A question comes to mind i.e., how deep is this iceberg and what is beneath the water line that we don't see?
- Imagine this is an iceberg at the VW plant

Operational Excellence

- “We are what we repeatedly do. Excellence, then, is not an act but a habit.”

- Aristotle



Operational Excellence

- Use of knowledge management and quality risk management will enable a company to implement ICH Q10 effectively and successfully. These enablers will facilitate achievement of the objectives described in section II.D (1.5) above by providing the means for science and risk-based decisions related to product quality.

Guidance for Industry
Q10 Pharmaceutical Quality System
April 2010


Operational Excellence

- Use of knowledge management and quality risk management will enable a company to implement ICH Q10 effectively and successfully.
- These enablers will facilitate achievement of the objectives described in section II.D (1.5) above by providing the means for science- and risk-based decisions related to product quality.
- Management should determine and provide adequate and appropriate resources (human, financial, materials, facilities, and equipment) to implement and maintain the pharmaceutical quality system and continually improve its effectiveness.

Guidance for Industry
Q10 Pharmaceutical Quality System
April 2010

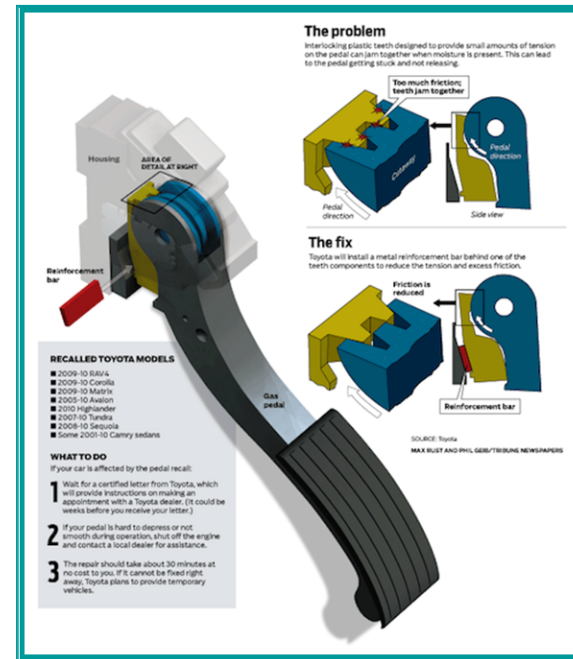
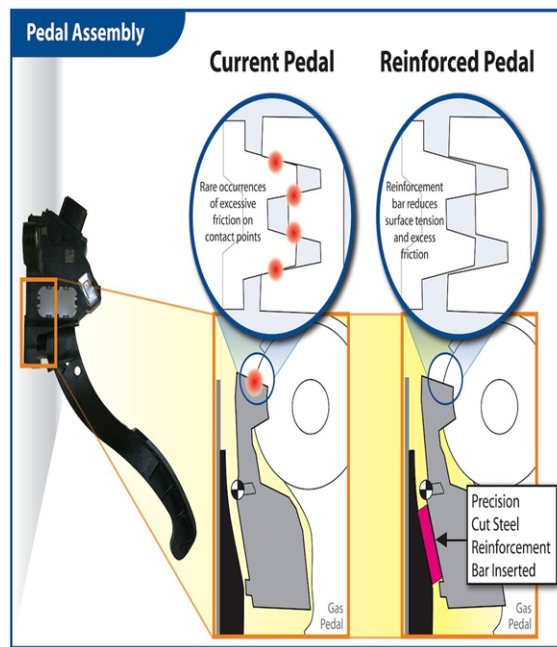
A need for Leadership

- “Leadership is essential to establish and maintain a company-wide commitment to quality and for the performance of the pharmaceutical quality system.”

 Q10 Pharmaceutical Quality Systems
ICH Guidance, June 2008

Toyota announces gas pedal fix

2/1/10 - CNN



Panel: Toyota didn't listen

USA Today

- Toyota's units haven't shared data adequately and that corporate structure delayed response "to quality and safety issues";
- Toyota "will be judged in the US as much by the quality of its decision-making as the quality of its vehicles"



Panel: Toyota didn't listen

USA – Today



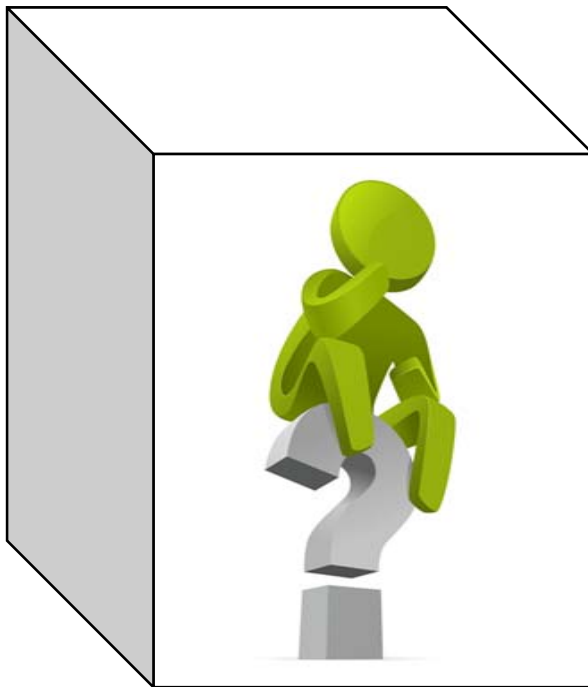
- Too centralized – to maximized control / decision making for
 - ✓ Recalls /Communications
 - ✓ Vehicle design and development
- Dismissive of outsiders
 - ✓ "Outsiders' complaints often have been ignored"
 - ✓ "sticky pedals" w/degree of skepticism
- Quick to equate safety with quality – the panel believes that safety and quality are different attributes

....I can't help but wonder...

- What are the pedal design considerations and acceptance criteria?
- Was the design criteria met?
- What departments/ organizations approved the final pedal design?
- What did we learn, and did we correct the issues to prevent further occurrences?



It is very difficult for those inside the box to think outside of it



- It is very difficult for an organization to see the truth about itself.
- Those inside a box can seldom see what is happening within it.
- It usually takes someone looking from the outside in to produce useful evaluations.

Management f-Laws how organizations really work

Triarchy Press, 2007- Russell L. Ackoff

Quality & Culture of Compliance

- Established from the top down
- Management must convey a commitment to compliance
- Management must actively work with Quality
- Quality needs clear management support
- Quality must convey a commitment to compliance
- Quality should constantly be working to better their operations

Quality & Culture of Compliance

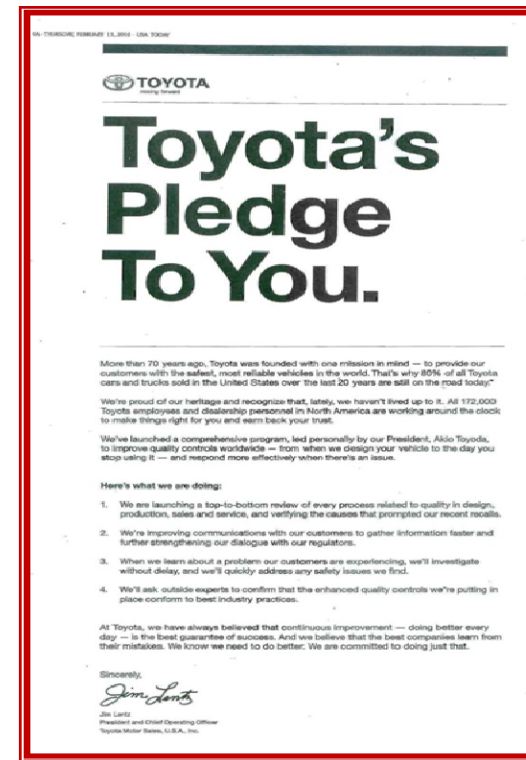
- All staff need clear and unambiguous understanding of their role
- Constantly reminded of this in everything they say and do
- Imagine that FDA is looking at everything
- Company culture is established from the top down
- Establish & demonstrate clear policies regarding
 - GMP's
 - Data integrity

Quality & Culture of Compliance

- Management must convey a commitment to compliance
- Must be perceived as
 - In control
 - Compliance minded
 - Intolerant of any non-compliance
 - Understanding
- Quality needs clear management support
- Quality must be perceived by Management & Staff to be
 - Authoritative
 - Responsible
 - Reliable
 - Confident
 - Proactive
 - Responsive

USA Today - February 11, 2010

- ...it may be the new Toyota Leadership...
- **Top-down** review of every process related to
 - quality of design,
 - production,
 - sales and service, and
 - verifying the causes that prompted our recent recalls



the Wall Street Journal — March 31,
2010

[illegible]

Toyota Bolsters Its Quality Control

- Intensified its QC campaign following global recall of 8.5 million vehicles.
- The actions are in part intended to deal with criticism that Toyota acted too slowly in response to its recent safety problems.
- Under new structure, headquarters will decide with counterparts in each region how to address quality issues,
- while chief quality officer in each market will share information about local customers' complaints.

What does the auto industry have anything to do with the pharma industry?

Questions –

- Who/what departments are part of ~~Toyota's~~ **your** Quality Unit?
- Do you have all the right people / departments at the Quality Unit table?
- Who/what department is not at your Quality Unit table? and,
- If not why not?



This leads us back to a pharma Quality System Coverage

- Product reviews (APRs)
- Complaint reviews
- Discrepancy & failure investigations
- Reprocess & rework
- Returns & salvage
- Rejects
- Stability failures
- Quarantine
- Validation status
- Employee training/qualification

Quality

- Responsible for Policies and Procedures
- Is “FDA” in the firm when FDA is not there
- Both Management & Staff should know and respect Quality
- Quality should be considered essential & not an added burden
- Everyone is responsible, no one is immune, this would include for example;
 - ✓ shop floor staff,
 - ✓ supervisors,
 - ✓ managers,
 - ✓ Directors and company Leadership
- It should be considered routine for all to report their findings
- There should be no negative consequence when findings are reported

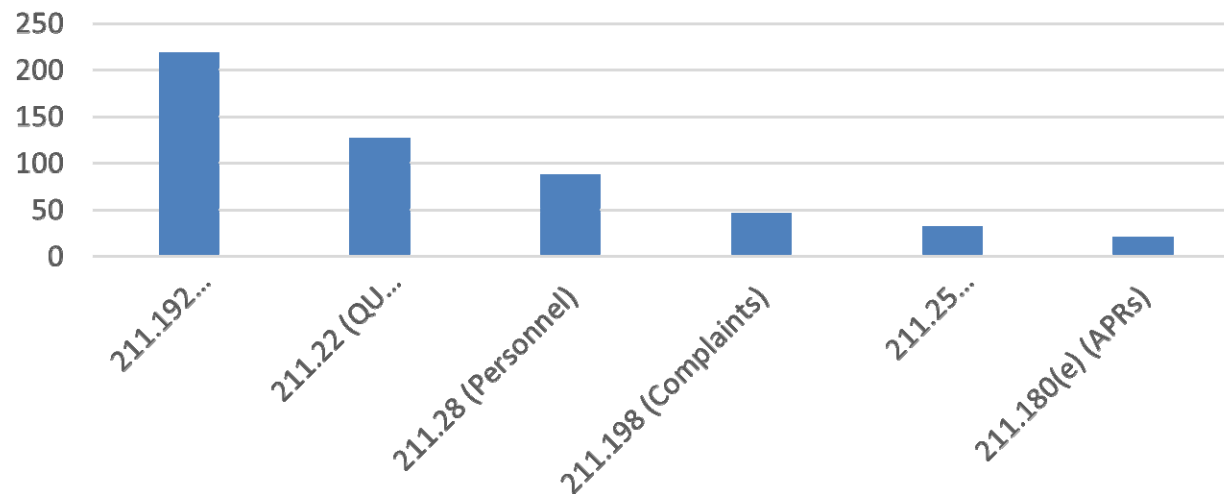
Top 10 Observation



21 CFR 211.22(d)

- The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed].

Quality cites supported in WLs 2008- March 2018



Quality



“Integrity is doing the right thing even when no one is watching.”

- C.S. Lewis



Dhanyavad

Thomas J. Arista
Deputy Director
U.S. Food & Drug Administration
US Embassy New Delhi, India
Tele. No. +91 11 2419 8085
Email – Thomas.Arista@FDA.HHS.GOV