“Emergence without Emergency”
Build and Maintain an Effective pQMS
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DG Shah: Indian pharma loses a significant voice on international trade and policy

PT Jyothi Datta | Mumbai | Updated on February 22, 2019 | Published on February 22, 2019

The Indian pharmaceutical industry’s annual conclave next week will miss a significant voice following the passing of DG Shah on Friday.

“The topic is perfect. The “maintenance” is more challenging and needs expert insight.” Dilip
It's not the years in life that count; it's the life in years.

Work and collaborate in cross functional teams

Function efficiently and independently in a constantly evolving environment.

In a fast pace, dynamic team setting.

Selected guidelines are illustrative
Level of “Assurance” determines what we experience; including therapeutic outcomes

To assure others one must be self-assured

Experiential learning is a path to adult development

Objective self-authorship at every level of a system provides subjective self-assurance to all its stakeholders

System responsiveness is a stage in collective human (adult)development – Order of Consciousness
Why metamorphosis to meaningful experience necessary

*To err is human, professional development via design & systems thinking*
What is Good Practice?

"All models are wrong, but some are useful" George Box (1978)
Observations of recurring errors and root cause “unknown”: “Common Cause”

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Responsibilities & Procedures for the QA Unit are not in writing or fully followed

Time to reduce error rate to “3.4 dpm” (Amgen)

How to break the 2-3 sigma barrier?

In 2015 FDA “informally” identified few companies, including Amgen (8)

Amgen (Martin VanTrieste) described path to 3.4 dpm, for every “CQA” and “CPP”; their journey took ~ 10 years (9)

Note: Before FDA push (2004) to “QbD”, Amgen using “QbD” tools (10)
In summary
What Amgen did (beyond QbD in R&D)) to reduce their error rate to 3.4 dpm

- Extensive analytical characterization of raw materials, manufacturing processes, and products; not just in the development phase but also, as needed, in the commercial setting (synthetic drug sector often scared of additional testing)

- Will of the management and their involvement to identify, track and control variation via process capability assessment

- Continually monitoring to ensuring robust analytical methods, manufacturing processes, and products (e.g., using industry benchmark for analytical variability and decreasing assay variability; relevant to Invalidated OOS Rate discussion to follow)

- Training, Qualification, Certification and Mentoring support to ensure flawless execution, and

- Focus on the supply chain - controls and confidence (not purchase department finding the cheapest “Certificate of Analysis”).
Human Performance: Evidence based performance, performance based management, pay for performance not just “results”

• Martin graciously reviewed and confirmed its accuracy. He suggested that it would be useful to add - on human performance - that a lot of the system incorporated learning from systems used by the United States Nuclear Navy (7 August 2017)
System responsiveness is a stage in adult development!

Hussain, A. S. How To Break the Pharmaceutical 2-3 Sigma Barrier (Like Amgen). PHARMACEUTICAL ONLINE. Guest Column I September 18, 2017
Dogmas & assumptions: Variable awareness

Errors of commission and errors of omission

• We say we approve a drug (when we actually approve a drug product); NDA, ANDA. We have been making “pills” for thousands of years; why need Development Report (ICH Q8)?

• “Pivotal” clinical and bioequivalence; trumps pharmaceutical equivalence. SUPAC Defaults are justified knowledge, e.g., 10X scale-up factor.

• We believe excipients are “Inactive Ingredients”; compendial purity and impurity profiles sufficient for ‘Certificate of Analysis” while most dosage form manufacturing is a “physical” process.

• USP monograph sufficient prior knowledge to develop generics; “attractor” - file first for 180-day exclusivity (an important “attractor” in our system)

• We believe verification criteria for Compendial test methods, particularly for physical attributes, ensures their stability and capability in a QC laboratory

• That traditional 3-batch “Process Validation” (PQ) ensured processes are “stable and capable” (while we struggle to implement FDA’s 2011 Guidance, in part, because of dogmas in CMC Review)

• We discount the impact of Recalls, Warning Letters and Import Alerts on patients, because we believe they cause no adverse effects to patients, and placebo and nocebo effects are “removed” during clinical trials and, therefore, irrelevant in real-world
Examples: Awareness – disorienting dilemma

- Adhesive failure and accidental deaths due to Fentanyl TDS (1995-)
- A system too dependent on “whistleblowers”
- “Check-the box”; adhesive not critical for an “adhesive” TDS!
- Unverified assumption in “validated” analytical methods

2/8/2019
Lecture @ IMT Mines Albi 14 November 2018. Ajaz S. Hussain, Ph.D. © 2018
FDA Regulation of Drug Quality: New Challenges

Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research, Food and Drug Administration
April 9, 2002

EXAMPLE

- Assuming normal distribution, with mean 100% and sigma = 6%,
- Probability (batch passes USP) = 0.957
- Means about 4% of batches fail although they are no different than the passing batches

Major Barrier to Adoption:

- Industry Concern About Regulatory Implications of Results
- Closer scrutiny will reveal variations in existing products missed by sampling
- Delay in approval of new product

Regulation of Drug Quality: Opportunity

- Empirical methods are probably approaching their theoretical maximum effectiveness
- New scientific understanding & new technologies can provide science-based approaches
- Plan: Use PAT as model
pQMS connects practice, research, policy & power to “Do Good”
Where ontological conflicts exist attention to representational practices and epistemology, however important, are insufficient.
My experiential learning

Inability to measure is a powerful reason to believe and say “it is not my problem!”

Where ontological conflicts exist, attention to representational practices and epistemology, however important, are insufficient.
Marketing Authorization plus “Good Practices”

Primum non nocere: First, to do no harm.

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**Common sense**

*01 Simple system*
- Best practices

*02 Complicated system*
- Good practices

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*Errors of commission.*

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*03 Complex system*
- Research, experimentation

*04 Chaotic system*
- Attractors with a “line in the sand”

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*Errors of omission.*

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*Cause → Effect: Self-evident*

*Cause & Effect: Expertise*

*Cause ? Effect: Experiments*

*Innovation, Butterfly Effect, Jugaad*

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Therapeutic Equivalence & Therapeutic Outcomes

• By definition Therapeutic Equivalence is an “expectations” - four parts, pharmaceutical equivalence, label, CGMP, when necessary bioequivalence

• “Pivotal bio” mindset is “common” and a reason for recurring errors which erode trust patients

• Understanding and practicing “totality of evidence” is difficult for many

• A systems or “Totality of Evidence” mindset, not “pivotal bio”, can and must be the path forward!

• QbD = Pharmaceutical Equivalence → reproducible BE & Process Validation → repeatable CGMP → Continuous Improvement → 6 σ
Value information about a drug (such as the price tag) can strongly affect its therapeutic effect.
Assurance of Therapeutic Equivalence

In the 21st century, real-world evidence will matter more and more

- “Today, patients feel like guinea pigs”
- “Since the beginning, Merck explains that they reformulated this medication at the request of ANSM …” (18)
- A “canary in the mind”
- On-going saga – “levothyroxine”
“Several European countries have seen major health issues after a switch from one levothyroxine brand to another, as well as following the introduction of several levothyroxine formulation changes.

Testing bioequivalence does not guarantee continued euthyroidism after a formulation change of levothyroxine.

…..increased prevalence of side effects as well as increased prevalence of biochemical signs of inadequate dosing, and result in increased health-care consumption and health-care expenses.

In at least 3 European countries, formulation changes have been introduced by manufacturers without adequate communication…..”

(19)
Reducing “information understanding asymmetry”

In the experience economy, the more you know, the more you NO!

Common cause: To build trust

- Trust
  - To accept a vulnerable position, assuming the best interests and competence of the other.
- Mind is as real as matter
  - Common sense is not so common
A canary tweeting in my mind!

• “With U.S. Generic Drug Market in Chaos, Indian Upstarts Rise”.
  • Bloomberg, 2017 (21)

• We are surrounded by “Fake News”, Conspiracies and the Matrix memes:
  • Red Pill: Brutal truths of reality, knowledge, freedom, ...
  • Blue Pill: Blissful ignorance of illusion, false sense of security, ...

@SGottlebFDA

Some pills are red,
Some pills are blue,
All are safe and effective,
If they undergo FDA review.

10:05 AM · 2/14/19 · Twitter for iPhone
Brands personalizing & “Indian Upstarts Rise”

Personalize professional development to reduce errors of commission & omission!
Chaos is not disorder, patterns, beyond average, not predictable (sensitivity to initial conditions), “strange attractors”: “Adherence” a fractal?
Healthcare sectors

- Electronic Medical Records
- Quality improvement programs
  - Example – fractal-based quality management infrastructure, lean six sigma, at Johns Hopkins
- Patient satisfaction, outcome and sustainability metrics
- Professional Development
  - Need to change the current culture of continuing education to focus on Continuous Professional Development (IOM, 2010)
“reImagine”
The case of a “Indian upstart” company

- January 07, 2015: A upstart sought advice on “Proactive assurance of data integrity”; no Warning Letter, their previous FDA inspection was in 2012.
- Through data forensics audit by external experts
- Self-author follow-up evidence based CAPA and solutions, i.e., no “CGMP Consultants”
- The MD and leadership to undergo Culture of Quality Training, sign Code of Conduct and Pledge, “no finger pointing”, draw a “line in the sand” to move ahead
reImagine a bigger box: “In the Box Thinking”

- US FDA Inspections: Operations
  - 2015: No observations (investigator informed of on-going metamorphosis)
  - 2018: No observations

- US FDA Inspections: R&D
  - 2016: 5 Observations, addressed rapidly + CLP
  - 2019: No observations

- Current state
  - Confidence building, but an FDA inspection still is a “major event”. Target it should be a routine, i.e. no additional preparation needed, a reconfirmation.
  - Increased business complexity, continual staff turn-over, palpable stress
Organizations fail or decline more frequently because of what they did not do than because of what they did. Russell L. Ackoff

In budget and time constraints, we must expand the scope (of projects & responsibilities) to minimize errors of omission in all functions: New + “New Prior Knowledge”
Build trust relationships


Human Vaccines & Immunotherapeutic (2018) (25)
Continuous Improvement & Development?

Mind is as real as matter: Personalize “PDCA” cycle to “PDSA” spiral

- Appreciation for systems requires a higher “Order of Consciousness” (6)
Experience (noun) is practical contact with events and objects in the “real world”; experience (verb) is to feel (emotions)

But, feelings (of emotions) are personal - “not professional”!

Disorienting dilemma induces dissonance and sparks awareness of a need to do; to act.

To engineer a solution one must be able to measure. Inability to measure becomes an excuse for inaction.

*Experiential insights not illusions: Experiential learning!*
• Design & Systems Thinking: ICH Q8 – 11 Guidelines
• Experiential learning by improving awareness of how we accumulate knowledge by creating learning space in our feeling space
• Inspiration, in parts, from Rumi’s Elephant in the Dark, Dr. Deming’s contributions, the Institute of Medicine (USA) reports starting with to Err is Human (1999), Fractal Approach to Quality Management System @ Johns Hopkins in Baltimore, and Prof. Kegan’s Orders of Consciousness as introduced his book “In Over our Head” (1995).
A Model of Pharmaceutical Quality System:
ICH Q.10 Guideline in EU and Guidance in the US: “Current Thinking”

“My Responsibility”
Personalize Development: Satisfaction Management
Satisfaction in adherence when compliance is to self-authored routines and SOPs!
India’s aspiration to be the ‘Pharmacy of the World’ is credible, palpable and indispensable!

- India already is and will continue to progress as one of the major economies of the world
- Let this journey accelerate
- Pharma quality assurance in 21st century: Sharper focus needed on education, training and experience (27)

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<th>Insight 2013</th>
<th>Where are we in 2016?</th>
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<tr>
<td>Perceptions about quality can change efficacy and safety of a drug product via placebo and nocebo effects.</td>
<td>Evidence on the significance of perception factors, and placebo/nocebo effects, emerged very prominently, particularly in the US, and the US FDA had to issue a final guidance highlighting the importance of colour and shape of tablets have on adherence rates.</td>
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<td>Remediation of cGMP issues is often difficult and is an expensive challenge.</td>
<td>CGMP remediation, particularly as it relates to US FDA Warning Letter and Import Alerts, are on-going with very few exceptions and other companies have been added to this list.</td>
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| Leaders should consider working together in pre-competitive space to strengthen training and education, and, for creating venues for dialogue with regulators to improve understanding and to seek out solutions to common challenges. | Leaders of India’s pharma sector have taken significant steps to collaborate and to engage with global regulators and are outlining a plan- “Quality Excellence”.

With the active encouragement of the US FDA, there is visible progress in the area of continuous monitoring and manufacturing of pharma APIs and products in an integrated manner – a potential shift in paradigm in the making.

Increasingly patients across the globe will ask the question “who makes the drug I take”; and trust and credibility will be critical.

Automated continuous manufacturing is now rapidly becoming a reality in the US and Europe, tipping point was reached in 2015. Significant collaborations have been announced among major companies.

Media coverage of FDA Warning Letters and Import Alerts have continued to be a source of concern.
Learning to experience: Actions and Reactions

*Input, Processing, Output with Feedback*

- Insights that can be useful to build and maintain pQMS in the real world context of 21st Century Quality and Cures
- Insights gathered from a conscious personal journey and contemporaneously noted, much shared in mainstream and social media starting with: “Strategies for making high pharma quality affordable.” Express Pharma. 2 November 2013 (28) and “Schrödinger’s Cat & My Journey From 2015 to 2020.” LinkedIn 23 December 2014 (29)
- The journey began in India in 2013, to date involved learning interactions with over 10,000 pharmaceutical practitioners in India, North and South America, Europe, Middle-east, Africa, Japan, South Korea, and China
- Stations included BAD-I Warning Letters, Import Alerts, Dispute Resolutions, Expert Witness Testimonies, Culture of Quality, CRLs, Quality by Design and Professional Development
As the 2015-2020 journey ends: Motivation

I wish for a “Butterfly Effect”: “Satisfaction in Adherence” is a common “adult” fractal

- A self-organizing system that manages pharmaceutical quality and gives assurance to patients and supports organizational learning and empowers professional development.

- From the fractal patterns of snowflakes to cellular lifeforms, complex patterns emerge.

- “Emergence” describes the ability of individual components of a large system to work together to give rise to dramatic and diverse behaviour (30).

- Creating a fractal-based quality management infrastructure (at Johns Hopkins Hospital System) (22).
## Summary: Manage variability, uncertainty and science & technology

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<th>Mode of Response</th>
<th>Key Focus Areas</th>
<th>System Modification</th>
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| **Operational**  | CAPA, Efficiency, etc. – Learning to R&D | Control of excipients and other sources of “common cause” variability &  
Reduce CGMP Risk Classification – Continuous Improvement of Quality System |
| **Tactical**     | Statistical Process Control (Technology & Knowledge Transfer) | Critical Control Points - Robust process endpoint &  
Reg. CMC Approval |
| **Strategic**    | Science of Design Technology Management Business Case | Sci. & Tech. Integration – Continuous Learning & Improvement &  
Regulatory Communication & Integrate Sci - Enabling Technology Platform – “Plug & Play” &  
“Time to Market” + “Production Efficiency” |

**About a decade ago.**
Invest in continual human development, professional development can be personalized by internalizing in our mind what we do to ensure our processes are suitable and capable. Improve design and systems thinking which are key to success in the revolution - Industry 4.0 or SmartFactory!

- As Dicken’s noted - This can be the age of wisdom or the age of foolishness, ... a season of light and season of darkness, the spring of hope and the winter of despair, ....

- And like the heroes of the French Revolution, we look to a future that will bring us everything or nothing, depending on the public trust.
To give assurance one must be self-assured

- Quality by Design, Quality System & Continual Improvement linked to Continuous PD
- Internal and External (real world) Validation
- First in, last out (market) with evidence of “Six Sigma Quality” (3.4 dpm) is sustainable success
- Education, training and experience
  - Experience (feeling and learning hour by hour; not “years of experience”) is the key to PD
- Systems orientation is a stage in adult development
pQMS
Pharmaceutical Quality Management System

• A rule-based corporate system, nested within other hierarchical systems, that is built and maintained to consistently provide pharmaceuticals conforming to regulatory specifications with the assurance needed to continually reaffirm claims endorsed by public health officials to satisfy expectations of profit seekers, patients, public, and professional practitioners

  • Quality assurance allows patients to accept a vulnerable position by assuming their best interests and competence of professional practitioners and public health officials
  • Evidence based rules and practices curtail human irrationality
  • Education and training of adults is diverse and their experiences personal
  • Asymmetries of information, knowledge, and understanding of reality will persist (increase)
  • Beyond continuing education and training is adult & professional development (PD): Self-authorship to be self-assured in increasing complexity
For additional information

For additional information

• The references cited, (1) to (30), are available on the internet. When requesting additional information on a particular reference please specify its number in email.

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