Pharmaceutical Technology, Education and Confidence in Assurance of Quality

Ajaz S. Hussain, Ph.D., President
The National Institute of Pharmaceutical Technology & Education, Inc.
Declaring my interests

Insight Advice & Solutions LLC

Advisory and Consulting Practice
Complex Generics, Biosimilars & Orphan Drugs
Advisory Boards: Several Companies
When requested:
Systems approach - CGMP Remediation (strategy)
Culture of Pharmaceutical Quality Training
with Emphasis on Data Integrity

President
Share my understanding of challenges in the assurance of "Pharmaceutical Quality"
Strategic planning and NIPTE advocacy.
Programming and other executive functions.
### Background: QbD Paradigm – Methodology – gaps

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Quote/Ref</th>
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<tbody>
<tr>
<td>1987: QbD Paradigm</td>
<td>“quality cannot be tested into products it has to be built in by design.”</td>
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<td>“Just refining procedures and documentation wasn’t going to change that.” Janet Woodcock</td>
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<td>Current state: QbD Methodology</td>
<td>Case example: Biotech “Tipping Point”</td>
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<td>Case example: Solid dose manufacturing: “Angle of Repose” &amp; “Tipping Point”</td>
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Assurance, a positive declaration intended to give confidence

Without a mechanism for the positive declaration, we have to work to reduce Warning Letters, recalls, shortages, delayed approvals,…

• The role of “Pharmaceutical Technology & Education” not adequately recognized (e.g., via a public funding mechanism)
• NIPTE was formed in 2005 to find ways to address this challenge; funding from US FDA UO1 granting mechanism
• NIPTE 2016 Conference to review, reflect and plan for the future
• What was NIPTE’s contribution? What are current hurdles and challenges? What can we learn? What can NIPTE do next?
Challenges: As described recently by FDA/CDER
Formation of the Office of Pharmaceutical Quality & Emphasis on One Quality Voice (12/2015)

Product recall and defect reporting data demonstrate unacceptably high occurrences of problems attributed to inherent defects in product and process design

Alarming shortages of critical drugs over the past few years

Rapidly growing numbers of Post-Approval Supplements; which inhibit industry’s ability to optimize and improve

Current regulatory review and inspection practices continue to be “one size fits all”; i.e., not considering specific risks to the consumer from product failure modes

There are no formal benchmarks for the current state of pharmaceutical quality; inadequate quality surveillance adds to the challenges that make it difficult to make decisions on risk

Inspection and Review functions remain disjointed; inspections not well-connected to knowledge gained from product application review and vice versa.

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<tr>
<th>Why?</th>
<th>Continued challenges in the assurance of &quot;Pharmaceutical Quality&quot;</th>
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<td>How?</td>
<td>Understanding the interaction of uncertainty, complexity and the crucial human factor in the assurance of quality</td>
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<td>What?</td>
<td>A framework to classify, at appropriate levels, the gaps that should be filled to address challenges</td>
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Outline

Case example: Biotech “Tipping Point”

Case example: Solid dose manufacturing: “Angle of Repose” & “Tipping Point”

How to make it normal easy and rewarding: effective integration & utility of PAT Guidance, ICH Q8-11 (12) – Process Validation with other guidances: Risk Mitigation, QMS, Knowledge Mgmt.

Understanding the interaction of uncertainty, complexity and the crucial human factor in the assurance of quality

A framework to classify, at appropriate levels, the gaps that need to filled to address the challenges that keep us in a reactive mode
A Biotech “Tipping Point”: Effective CAPA to Continuous Improvement

“If I don’t look there is no problem” - Problem-solving - Prevention of errors

3 September 2003
THE WALL STREET JOURNAL.

Factory Shift
New Prescription for Drug Makers: Update the Plants
By: Leila Abboud & Scott Hensley
“...the pharmaceutical industry has a little secret: Even as it invents futuristic new drugs, its manufacturing techniques, lag far behind those of potato-chip and laundry-soap makers.”

Why are Investigations Important? Stuff Happens!

We are here to serve patients

Amgen has been on a Continuous Improvement Journey

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
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<tbody>
<tr>
<td>2006</td>
<td>Instituted Risk Based Classification System &amp; Class 1 Quick Close Process</td>
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<td>2007</td>
<td>Improved Trending of Nonconformances</td>
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<tr>
<td>2008</td>
<td>Improved Management Review, Developed Network Metric Control Plans</td>
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<tr>
<td>2010</td>
<td>Standardized Root Cause Analysis</td>
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<tr>
<td>2011</td>
<td>Developed Technical Writing Course for Investigators, Involved Quality Sciences in Investigations</td>
</tr>
<tr>
<td>2012</td>
<td>Initiated Investigator Mentoring, Qualification &amp; Certification Program</td>
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</table>

Martin VanTrieste, R. Ph. Improving the Quality of Investigations. PIA Meeting – June 21, 2012
Disclaimer

• The case example of Amgen and Vertex are for illustration purpose
  • I am aware of several other companies that are on the same path (and may not have shared their information publicly)
  • I have no association with either company nor have I any basis to verify their claims
  • Selection of the case examples was motivated because it makes good sense, have been shared publicly and also included in presentations and press interviews by leaders at FDA (recognizing that this does not necessarily reflect the FDA’s opinion)
Solid Dosage Form Manufacturing: “Tipping Point” not feasible without an “Angle of Repose”

- Certificate of Analysis
  - Uncertainty in solid-state material attributes
- Research laboratory measurement systems
  - Life-cycle stability and reproducibility in QC?
- Fixed equipment and process parameters
  - Committed in submissions, difficult to change post approval; why bother finding the real cause?
- Uncertainty in the stability and capability of measurements and manufacturing process
  - Raises questions on adequacy of sampling and obstructs risk-based decisions
- Globalization – variable empowerment/oversight
  - “FDA Approved” and “Validated”; frames the mindset and provides reasons to rationalization
Repeating deviations and errors & ineffective investigations
Weak epistemology and risk of irrational behaviors
“Angle of Repose”: Adaptive learning challenges

Solid Oral Dosage Form Manufacturing

At a Tipping Point

- NDA 26038; Orkambi®, Vertex Pharmaceuticals. 25 June 2015
- Post-approval change: NDA 021976 Prezista®, Janssen. 12 April 2016 (Continuous manufacturing with RTRT)

Progress and set-backs

- Several, ....others (new drugs); generics faced OGD push-back
- 2006 MSD/Merck

The Beginning

- 2004-2005 Sanofi-Aventis Comparability Protocol (FDA Approved - Not Implemented)
- (Late 1990’s: Medical Gas; Air Separation Units)
Angle of Repose & Tipping Point

From “Don’t use or Don’t tell”* to problem-solving mindset,......

PAT-Continuous Manufacturing – RTRT platforms for rapid product development, control strategy, and Design Space

1. Angle of Repose
   Loss in Weight (LIW) Feeders
   - Loss-in-Weight (LIW) feeders dose individual components: intra-granular (IG) blend and final blend components
   - Continuous real time measure of mass flow used to maintain set point, desired precision and IPC measurement

2. Tipping Point
   PAT Methods Sample a Large Percentage of the Batch

3. From: Martin Warman, Kelly Swinney and Justin Pritchard. PAT for In Process Control (IPC) and Real Time Release Testing (RTRT) in Continuous Manufacturing. 7th Pharmaceutical Technology Conference on Continuous Manufacturing, Japan (December 2015)
   http://www.fda.gov/ohrms/dockets/ac/02/briefing/3841B1_05_PFIZER.PDF; FDA Science Board 16 November 2001

Multiple companies and Schools passionately perusing this opportunity with regulatory encouragement and acknowledgment of its potential for higher level of assurance

Enforcement of Continued Process Verification (PV 2011) now becoming apparent in the USA; adds an emphasis on statistical confidence and process stability and capability

Example PAT Locations Available for IPC and RTRT

NIR
Laser Diffraction
Loss in Weight
Feeders

NIR

Analysis of a hand full of tablets by Regulatory QC Methods
PAT data collected repeatedly during manufacture

PAT methods sample a significantly larger percentage of the batch providing an appropriate assessment of in-process materials and batch quality
Angle of Repose and Tipping Point:

**Angle of Repose**
- At this angle, the material on the slope face is on the verge of sliding
- Technical Solutions & Education

**Law of the Few, the Stickiness Factor and the Power of Context** [Malcolm Gladwell]

**Tipping Point: 10% by 2020**
- When a group rapidly and dramatically changes its behavior by widely adopting a previously rare practice
- Fear/penalty of large sample size in QA removed

Law of the Few, the Stickiness Factor and the Power of Context [Malcolm Gladwell]
Angle of Repose to Tipping Point: Journey* needs to now go from extraordinary to normal, easy and rewarding

Technical Learning

• Material science, methods & knowledge management
• Control strategies (with “new” measurement systems)
• Engineering skills
• Statistics (Chemometrics; large sample size)

Adaptive Learning

• Culture/Mindset change: reactive to proactive (with statistical confidence)
• Cross-functional collaboration
• Systems thinking, understanding effective QMS, and change management system

*Effective control strategy & risk-mitigation to improve confidence in assurance of quality
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How to make it normal easy and rewarding: effective integration & utility of PAT Guidance, ICH Q8-11 (12) – Process Validation with other guidances: Risk Mitigation, QMS, Knowledge Mgmt.

Understanding the interaction of uncertainty, complexity and the crucial human factor in the assurance of quality

A framework to classify, at appropriate levels, the gaps that need to filled to address the challenges that keep us in a reactive mode
The Quality “thinking chain” and our set mind (legacy): How do we know what we know, when and why?

“….quality cannot be tested into products, in has to be built-in by design” → Quality by Design (QbD)

Process understanding and control in an effective QMS: Opportunity to optimize and improve

The human factor is crucial! ... Effective Quality Management System!
Uncertainty & Legacy Practices: Procrustean discriminating specifications and regulatory commitments in a submission

- **Procrustean** *(marked by an arbitrary, often ruthless disregard for individual differences, special circumstances, and/or prior knowledge)*
  - Prof. Leslie Benet (ACPS Meeting April 14, 2004): “The Current U.S. Procrustean Bioequivalence (BE) Guidelines”; “BCS is a non-Procrustean advance, we should consider other non-Procrustean advances”

- We often use “market standards” as batch release tests; penalty for large sample size
- Critical importance of repeatability and reproducibility of methods for physical quality attributes over a life-cycle in QC
- Root-cause often unknown; inability to distinguish between “common and special” causes

- Need to reconsider an integrated approach *(i.e., totality of evidence not just put all emphasis on one test)* to specification setting and do so before *(e.g., EOP2)* not after the product has been developed

> Therefore, we propose that the sponsor’s specification of Q=80% at 60 should be changed to a specification of Q=80% at 30 min.
How to make it normal easy and rewarding?

Recognize the Legacy Challenges

• 1993: GMP Lessons from a Federal Judge
  • “you can’t test a product into compliance”;
  • “the Court cannot rely on industry practice alone to determine whether an individual firm meets the statutory requirements”
  • “Industry can look for guidance to literature, from seminars, textbooks and reference books, and FDA letters to manufacturers”

• Uncertainty & Legacy Review Practices: Procrustean discriminating specifications and regulatory commitments in a submission

Integration of PAT, ICH Q8-11 (12) – Process Validation with other: One Quality Voice

• FDA 483’s, Warning Letters and Review Deficiencies are the predominate sources of “guidance”
• Reactive and promoting “cut-paste” approaches that take away from understanding (traps the system in the 3rd Order; not conducive to continual improvement)
• There are gaps in scientific literature, textbooks and reference books
• Difficult to reuse and generalize prior knowledge and data (e.g., lack of data on fundamental material attributes)
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Uncertainty, Risk and Quality Assurance: The crucial human factor – accounting for stress, errors, and irrational decisions

Quality complexity generally recognized and accounted for

Organization's accounting of: Complexity, Capability, Capacity, Time & Cost

Biotech → Biosimilar → New Drugs → Complex Generic → New Drug – Breakthrough Designation → Generic → First Generic

Recognition and accountability continuum: Optimal to sub-optimal

Education, Training & Experience: Frontline to Senior Management

Time- Cost reduction pressure on Company, FDA & Public Health

Continuum of cost reduction pressure: Low to high

Quality complexity generally recognized and accounted for

October 3, 2016
“If I don’t look there is no problem” - Problem-solving - Prevention of errors: Descriptors of organizational maturity

“I know it when I see it” to “I can see clearly now (2020)”

• Design Space, Procrustean, Epistemology (Intuition in 2000 to insight in 2015)

Pharmaceutical Quality as Elephant in the Dark

• Not Six Blind Men & the Elephant

Snakes & Ladder

• Adult Human Development & Human Irrationality (Behavioral Economics)

QbD Paradigm – (Ontology)-(Epistemology) – ICH Q8 Methodology – (Methods for QbD)
Case Studies & Changing our GXP set mind: Order of Consciousness and Continual Improvement

“Don’t use or don’t tell” and/or “If I don’t look there is no problem”

Immunity to Change

3rd Order

4th Order

5th Order

Problem-solving

Prevention of errors

Adult Human Development & Immunity to Change

*Prof. Kegan et al. Harvard University

Subjective to Objective: Reduce risk of irrationality
Focus on adult human development & cognitive biases: Epistemology is critical

5th Order: Self-Transforming Mind
Meta-leader, leads to learn, problem-finding, independent, multi-frames, holds contradictions

4th Order: Self-Authored Mind
Own compass/frame, agenda-driving, system thinking, problem solving, ego - empathy, learns to lead

3rd Order: Socialized Mind
Seeks direction, reliant on “FDA Guidance = Regulation”, “If I don’t look …”, “Don’t use…”

Risk of irrationality: Cognitive biases, framing effects, blind-pots, others.

Procrustes would be at 2nd Order

Real-time documentation and assurance of data integrity: A. L. C. O. A

Nobel Laureate Prof. Kahneman

QbD in neither new or unique; we must keep Procrustes (our irrationality) out to make the journey normal, easy and rewarding.

• We are standing on the shoulder of giants: Integrating Big Ideas
  • **Design space**
    • Fisher, Shewhart, Deming, Box, Juran,
  • **Procrustean** *(marked by an arbitrary, often ruthless disregard for individual differences, special circumstances, and/or prior knowledge)*
    • Prof. Kahneman (and others): Countering our cognitive biases and preventing irrational behaviors
  • **Epistemology**
    • Guided reflection, essential for adult human development, to raise our *Order of Consciousness*, and to overcome our *Immunity to Change* (Professor Kegan and others)
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QbD paradigm shaped the written CGMP regulations. ICH Q8 outlined a methodology, it did not invent QbD!

- Adherence to CGMP regulations is what FDA recommends (FDA website: Facts about CGMPS); yet we only adopt a ‘compliance’ mindset
- Compliance with company specific SOP’s is required; these are often written without process understanding; can be a source of many of our Procrustean behaviors
- Specifications and controls not set right can be Procrustean behaviors and a source of other Procrustean behaviors.
  - As these are often established by regulators after the product has been developed and trials conducted;
  - Often without the benefit of utilizing prior knowledge to inform what is critical to patients and product performance over its shelf-life
- Need for the risk-based approach; need some flexibility - Design Space!
- ICH Q8 only outlined a (scientific) methodology to communicate in Section P2 – CTD how quality was built –in by design
- In the USA, Development Reports – used to be left on site; CMC Review leadership, before the 21st Century Initiative, vehemently opposed considering knowledge that was (or could be) contained in Development Reports; why: “not scientific.”
### Gaps

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<tr>
<th>Paradigm</th>
<th>Common understanding of ‘Pharmaceutical Quality By Design’ – One Quality Voice (CMC, Clin. Pharm. Review (R&amp;D) to CGMP Inspections (Ops/QA) – as one Quality Management System</th>
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<tr>
<td>Ontology (assumptions &amp; blind spots)</td>
<td>Nature of (being) reality - What is pharmaceutical Quality, functionality &amp; CQA’s of materials (e.g., physical attributes) or the structure/organization of public pharmaceutical knowledge (for maximal generalizability &amp; reusability ?)</td>
</tr>
<tr>
<td>Epistemology (assumptions &amp; blind spots)</td>
<td>Theory of pharmaceutical knowledge (pre-formulation –formulation – process design – validation – CPV): How do we know that a method/process is validated? Risk is objectively assessed &amp; managed?</td>
</tr>
<tr>
<td>Methodology</td>
<td>Outlined in ICH Q8 for sharing (prior &amp; new) knowledge to establish risk-based controls and speciation’s and to realize timely commercialization via effective knowledge &amp; technology transfer ; statistical confidence and the weight of evidence.</td>
</tr>
<tr>
<td>Methods</td>
<td>New and more reliable methods for rapid, real-time, measurement of critical to quality attributes, ensuring their stability and capability characteristics over their life cycle.</td>
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**“not scientific” to a Framework to Classify Gaps**

Multi-disciplinary teams often have unaccounted differences in their ontological & epistemological assumptions.

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_October 3, 2016_  
FDA CDER White Oak, Building 31, Room 1503 (Final)
• Pharmaceutical quality decisions are made by multidisciplinary teams (a range of maturity), at different times and in various organizations; understanding of the QbD paradigm and methodology is derived experientially - One Quality Voice is hard to achieve!

• Legacy challenges, various ontological assumptions and weak epistemology curtails knowledge sharing, delays consensus and keeps us trapped in a reactive mode (3rd Order)

• The risk of irrational decision making needs to be accounted. "Cut-paste" or “check-the-box” practices are reminders that we are not achieving an optimal integration or practicing systems thinking.

• A reactive approach (3rd Order) to filling the noted gaps poses risk of continued erosion in the confidence the public should have in our assurance of pharmaceutical quality

• We need a thoughtful, planed approach to filling these gaps –NIPTe should take on this challenge!
Quality Assurance System: Global Supply Chain
What can NIPTE contribute?

Approach to filling the gaps and explain how the Nation will benefit: NIPTE Road Map 2016

Education & continuing education with assessment & certification (critical for adult human development)

Ontological analysis and standardization to facilitate and knowledge curation & sharing and systems for Knowledge management

Research to support development of 21st Century Methodologies & Methods (as exemplified at this conference)

Founded in 2005
Incorporated in 2007: 501(c)(3) Non-Profit Organization

13 Schools of Pharmacy, 3 Schools of Engineering, 1 Medical School

~ 10 year collaboration with FDA

Depth of multi-disciplinary expertise resulting from individual faculty members integrated voluntarily at scales that offer effective solutions.
Closing Thoughts: It is all about developing self and helping others do the same

**5th Order: Self-Transforming Mind**
Meta-leader, leads to learn, problem-finding, independent, multi-frames, holds contradictions

For me this has been a personal journey to reach a higher Order of Consciousness. The path I traveled @FDA was illuminated by a Self-Transforming Mind; Thank you Janet!

**3rd Order: Socialized Mind**
Seeks direction, reliant on “FDA Guidance = Regulation”, “If I don’t look ...”, “Don’t use...”

We shall not cease from exploration, and the end of all our exploring will be to arrive where we started and know the place for the first time. T. S. Eliot

**4th Order: Self-Authored Mind**
Own compass/frame, agenda-driving, system thinking, problem solving, ego - empathy, learns to lead

**System 1**
Thinking Fast
Automatic, Risk of irrationality

**System 2**
Thinking Slow
Analytic; “self -peer review” reason dominates

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