Pharmaceutical Quality Systems: US Perspective

Rick Friedman

Associate Director, Office of Manufacturing and Product Quality

Center for Drug Evaluation and Research

Topics

- Background: The ICH Q10 Pharmaceutical Quality System
- 21st Century Quality: What it Looks like
  - The Q10 Quality Culture
  - Business Case
  - State of Control
  - Modernization/Innovation
  - Root Causes

Background:

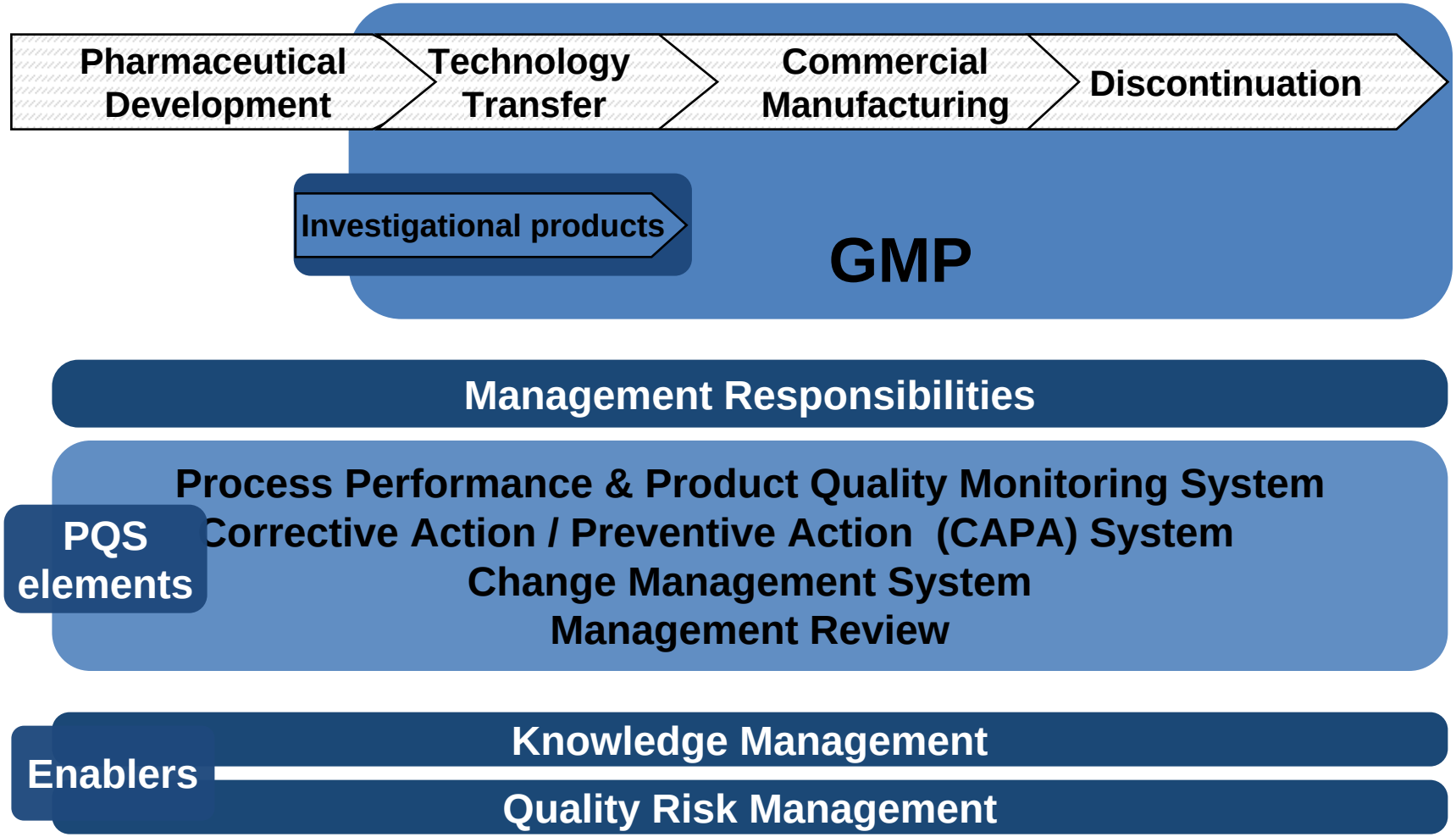
The ICH Q10 Pharmaceutical Quality System

Background: Pharmaceutical Quality System

- **Foundation:** Regional GMP (drug product) requirements, the ICH guidance "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," and ISO quality management system guidelines form the foundation for ICH Q10.
- **Harmonization**: ICH Q10 provides a harmonized model for a PQS.
- **Lifecycle:** Defines how a modern quality system assures science- and risk-based drug manufacturing and quality decisions throughout the lifecycle.

Background: Pharmaceutical Quality System

- Establish and maintain a State of Control
- Facilitate continual improvement
- Facilitate effective knowledge transfer and management
- Facilitate implementation & effective utilization of:
  - Quality by Design (Q8 Pharmaceutical Development)
  - Risk Management (Q9 Pharmaceutical Risk Management)


Pharmaceutical Development
Technology Transfer
Commercial Manufacturing
Discontinuation
Investigational products
GMP
Management Responsibilities
Process Performance & Product Quality Monitoring System
Corrective Action / Preventive Action (CAPA) System
Change Management System
Management Review
PQS elements
Knowledge Management
Quality Risk Management
Enablers

Background: Pharmaceutical Quality System

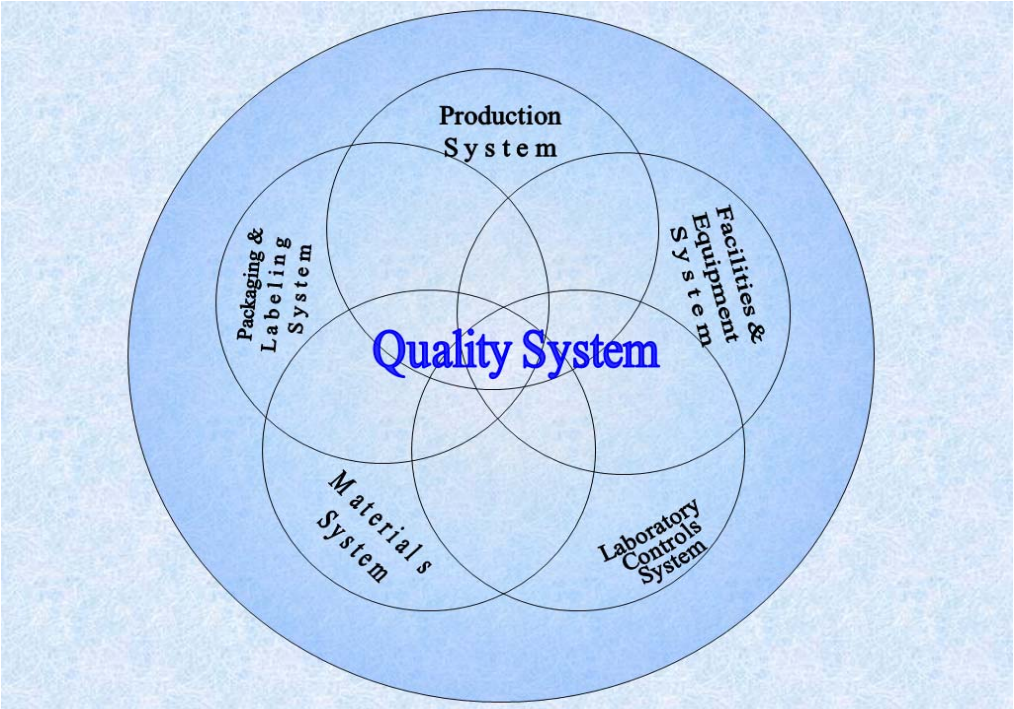
The pharmaceutical quality system "assures that the desired product quality is routinely met, suitable process performance is achieved, the set of controls are appropriate, improvement opportunities are identified and evaluated, and the body of knowledge is continually expanded."

ICH Q10, Section 3.1.3 Commercial Manufacturing

The Quality System:
Foundation for Assuring an Ongoing State of Control

FDA Inspection Program Includes:

- Materials System
- Equipment & Facilities
- Production
- Laboratory
- Packaging & Labeling
- Quality System

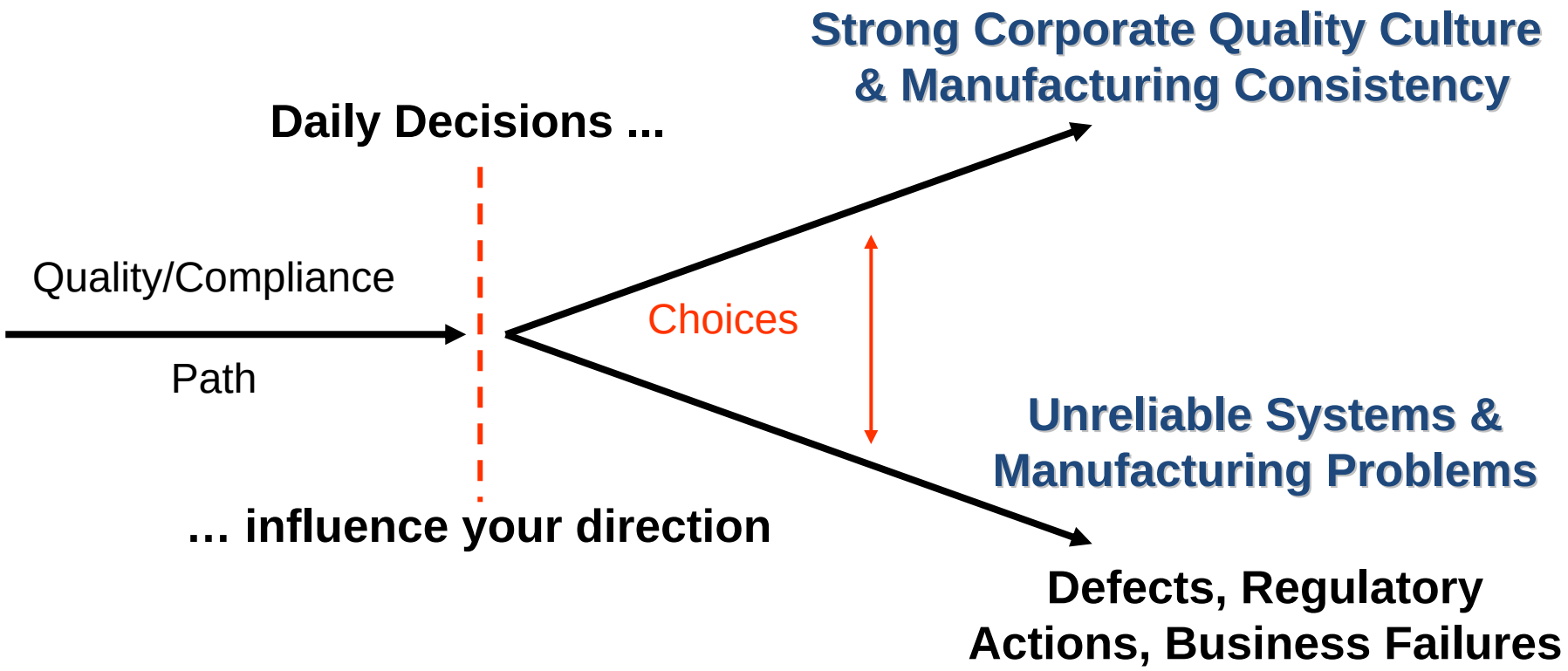


21st Century Quality: What it Looks Like

Words/Concepts you will hear frequently this week:

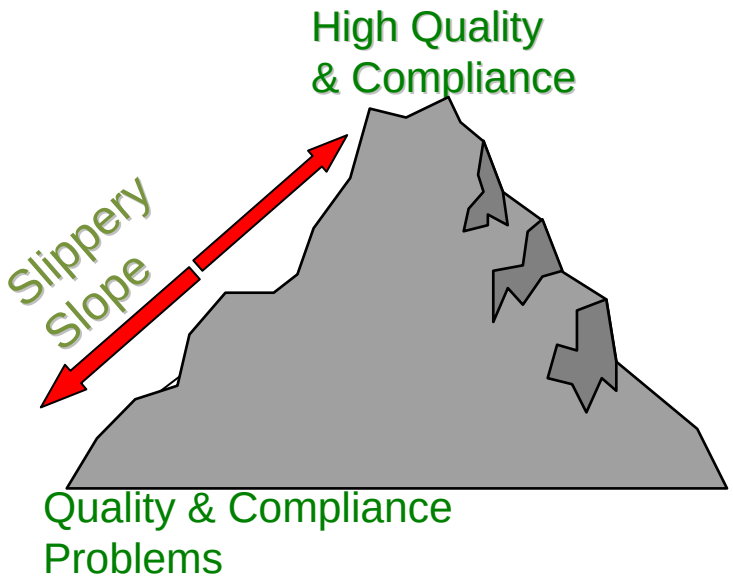
- Quality Culture
- Business Case for Pharmaceutical Quality
- Management Responsibility
- State of Control
- Innovation
- Root Cause
- Lifecycle
- Statistical Analysis
- Process performance and capability
- QC (reactive) vs. QA (preventive/proactive)
- Continual Improvement and Variability Reduction

Leadership and the Corporate Quality Culture



Adapted from Richard Davis (2004)

Quality Culture



- Support for the Quality Organization
- Actions More Than Words
- Investment in Quality
- Quality Involved in Relevant Business Decisions
- The Quality of the Work You Accept Becomes the Organization's Standard
- Organizational Structure: assures that QA is independent and not subordinate to other organizational unit

Adapted from Richard J. Davis

Quality Culture: These are all integral to continuous learning and improvement (includes supplier relationships) throughout the lifecycle:

1. *Science-based* approaches
2. Decisions based on *understanding product's intended use*
3. Proper identification and control of areas of *potential process weakness* (including raw materials)
4. *Responsive deviation and investigation systems* that lead to timely remediation
5. Sound methods for *assessing risk*
6. *Well-defined and designed processes and products*, from development through entire product life cycle.
7. *Systems for careful analyses* of product quality
8. *Supportive management (philosophically and financially)*

The Business Case

- **GMP is Good Business Practice**
  - PQS further aligns GMP with basic business goals of process predictability (e.g., Right First Time) & product dependability
- **Deming's Chain reaction**:
  - Reduce Variability → Improve Quality →Decrease Costs (rejected goods, etc.) → Better Products and Productivity… → More Competitive
- **Measuring Performance is Fundamental to Any Business**
  - **Actual Performance vs. Standard**: Identify process and product quality performance gaps, and promptly correct **root causes**
- **Prevention**
  - **Preventing manufacturing problems** is good business

State of Control / Variability Reduction at Core of Process Validation Guidance

Description of Activities	*Goals*
Stage 1: Process Design	
Lab, pilot, small scale and *scale-up* studies to establish process based on knowledge	Functional understanding between parameters (material and process) and quality attributes
Stage 2: Process Qualification	
▪ Facility, utilities and equipment ▪ Performance Qualification - evaluate adequacy of commercial process design - replication at full scale provides initial assurance of commercial process reliability	Scientific measurable evidence that ▪ commercial plant is capable of reproducibly meeting appropriate specifications, limits and standards
Stage 3: Continued Process Verification	
▪ Gain process experience and determine raw material and process variability/capability ▪**Monitor, collect information, assessment** ▪ **Maintain state of control**, continuous verification, adaptation, process improvement	▪ Gauge process reliability & better understand failure modes, including raw material inputs ▪*Prompt* actions to maintain or improve control (CAPA/continual improvement) ▪ Reduce product and process variability

Innovation

- Found 11 times in Q10. Some examples:
  - **Glossary:**

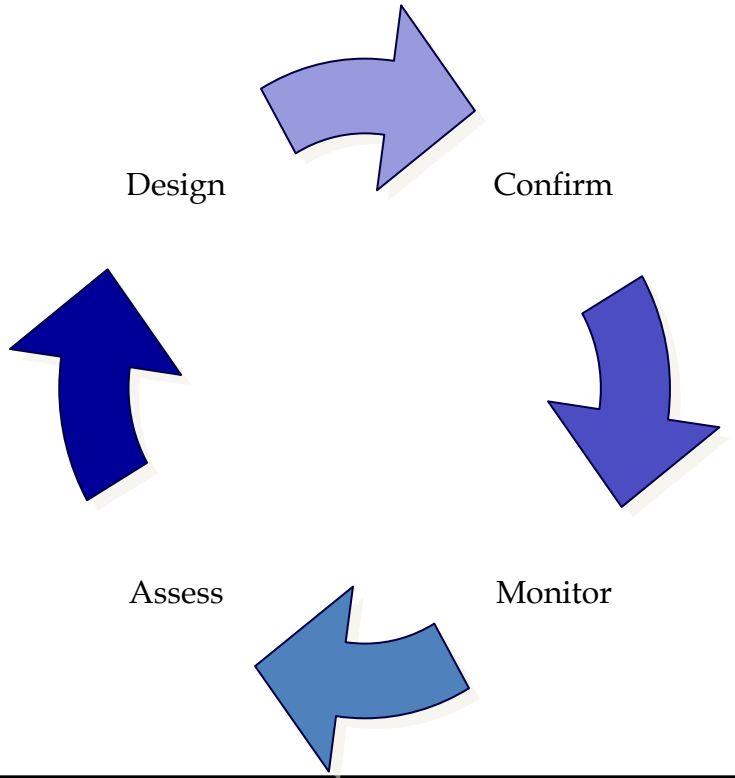
    Innovation: The introduction of new technologies or methodologies. (ICH Q10)

  - **Introduction:** Implementation of ICH Q10 throughout the product lifecycle should facilitate *innovation* and continual improvement

  - **Change Management (3.2.3)**: *Innovation*, continual improvement, the outputs of process performance and product quality monitoring, and CAPA *drive change.*

Innovation (cont'd)

Facilitate Continual Improvement (1.5.3):. Implement appropriate product quality improvements, process improvements, variability reduction, *innovations* and pharmaceutical quality system enhancements**.**



Innovation (cont'd)

- **Continual Improvement of the PQS (4.2)**: Innovations that might enhance the pharmaceutical quality system

- **Knowledge Management (1.6.1):** Sources of knowledge include, but are not limited to… manufacturing experience; *innovation*…"
  - Awareness of new opportunities for innovation, such as advanced technologies (manufacturing, analytical)

Innovation: Modern Pharmaceutical Manufacturing

"…significant opportunities exist for improving development, manufacturing, and quality assurance through innovation in product and process development, process analysis, and process control."

Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (2004)

Unit dose uniformity performed in-process (e.g., using weight variation coupled with near infrared (NIR) assay) can enable real time release testing and provide an increased level of quality assurance compared to the traditional end-product testing using compendial content uniformity standards.

ICH Q8

Innovation: Some examples of what Process Analytical Technology (PAT) can measure *in situ* or "*at line*"….

API process step endpoints
Residual Solvent levels
Particle Size
Identity
Granulation Progress and Completion
Drying Endpoint
Blend Uniformity
Content Uniformity
Assay
Weight
Hardness
Thickness

Determining the Root Cause of Quality Issues

Assuring quality each production day, each dose, for each patient

If you are operating at 3.8 Sigma, you are getting it right 99 percent of the time... It turns out that even a 1 percent error can add up to a lot of mistakes pretty fast. Getting it right 99 percent of the time is the equivalent of 20,000 lost articles of mail every hour. It's 5,000 botched surgical procedures every week. It's four accidents per day at major airports... If you can answer when, where and how often the defects occur you have what you need [to start to address the problem]... But don't just focus on the symptoms of the problem. Find the **root causes.**

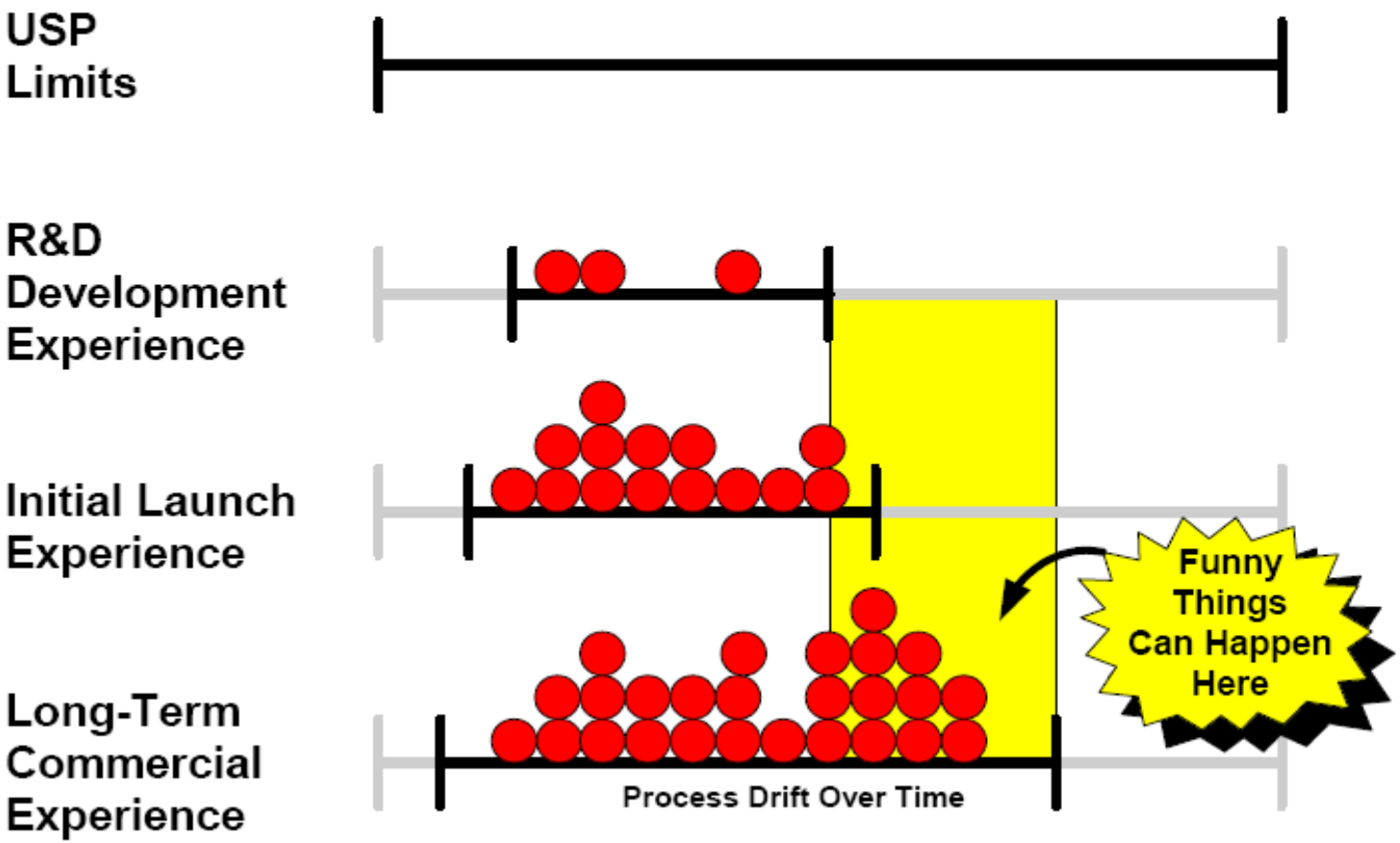
Chowdury, 2001

Determining the Root Causes:
Two "very" common causes…

- Human Error
  - Cause of substantial variation across the industry.
  - Can be prevented by analyzing process for failure modes and increasing automation.
    - "Human Error Analysis" – HE training allows for "deeper insights into the underlying causes of human error in order to identify and avoid its sources"

    [Miglaccio, et al, Chapter in The Pathway to Operational Excellence*, 2010, ECV Publishing]*
- Raw Materials
  - Excipients -- FDA's *Recall Root Cause Research* findings

Raw Materials: Typical Historical Experience with Physicochemical Properties



[Jean-Marie Geoffroy]

The Global Supply Chain: Responsibility Throughout the Supply Chain

All parties who manufacture (includes testing), process, pack, or hold an *ingredient* or *drug product* are responsible for meeting CGMP.

Adulterated Ingredient = Adulterated Drug Product

Recall Case Studies: Examples of Excipient Variability

- Excipient variation has resulted in several recent recalls due to poor dissolution:
  - Tablet lots had significant dissolution failures due to variation in the coating agent, **Zein NF (natural polymer derived from corn)**
  - Soft gel capsules failed dissolution as a result of **cross-linking of short chain aldehydes** and other liquid components
  - Extended release tablet failed dissolution due to variability of the **ethyl cellulose excipient**
  - Oral Powder for Suspension product failed dissolution due to the **Glyceryl Behenate acid value**

Case Study: MCC Morphology

- Microcrystalline cellulose from new source was initially found equivalent to original source

- Microcrystalline cellulose samples were later found to have meaningful morphological differences that led to dissolution failures
  - **some of the MCC lots had round particles, while others had long fibers**

- Lesson learned: Do not underestimate the impact of morphological characteristics on dissolution. Reinforces complexity of dissolution/disintegration attribute and importance of test.

CGMP: Every batch, Every day…

"We rely upon the manufacturing controls and standards to ensure that time and time again, lot after lot, year after year the same clinical profile will be delivered because the product will be the same in its quality… We have to think of the primary customers as people consuming that medicine and we have to think of the statute and what we are guaranteeing in there, that the drug *will continue to be safe and effective and perform as described in the label*."

- Janet Woodcock, M.D.