Engineering a Proactive Decision System for Pharmaceutical Quality: Integrating Science of Design, Process Analytical Technology and Quality System

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Reactive Vs. Proactive Decision System for Pharmaceutical Quality

- Reactive (examples)
  - Testing to document quality
  - Repeating deviation and out of specification investigations
  - Waiting for FDA guidance to submit ANDA demonstrating therapeutic equivalence of generic products
  - Potential for multiple NDA CMC review cycles
  - Waiting for FDA to approve a *prior approval supplement* for process optimization and continuous improvement efforts
  - Fear, apprehension
- Proactive (examples)
  - Quality by design and real time process controls to achieve real time release"
  - Right First Time
  - Innovative approaches for demonstrating therapeutic equivalence of generics
  - Single NDA CMC review cycle
  - Process optimization and continuous improvement efforts within a facilities quality system
  - Ability to utilize prior knowledge
  - Empowerment, recognition

Reactive to Proactive Journey is Very Challenging; Significant Rewards for…

- If this was easy we would have done it already
- The PAT – CGMP for the 21st Century Initiative opened a widow that shows some exciting opportunities and possibilities
  - A few companies appear to have found the door and have began planning for this journey, a handful have opened the door and embarked on this journey

Opening the door is probably the most difficult part

- Upper management support, commitment and decision-making
  - Commitment of resources today for results tomorrow
    - Always under uncertainty
- Have to overcome the inertia of traditions and culture
- Organizational barriers & “turf” issues
  - Collaboration and team approach a MUST

Initial Activity of Current Leaders Suggests

- It is easier to open the door for already approved products
  - Regulatory tools – PAT Guidance, Comparability Protocol, Quality System approach to CGMPs
- "Regulatory uncertainty" and fear of delayed approval is still very high (+ productivity improvement in production may not be an R&D goal)
- However significantly higher benefits expected when starting in development!
  - ICH Q8 – "design space", QbD, recasting process validation – process control using validated controls, Quality System approach to CGMPs

Reducing "Regulatory Uncertainty"

- Reduce uncertainty itself
- Understanding uncertainty from the regulators perspective
  - In general, post approval CMC regulatory concerns and decisions are predominantly managing "uncertainty"
  - Opportunity for risk-based decisions exists during the NDA review process, but high uncertainty due to limited (NDA's) or no development (design) information/knowledge (ANDA's) limits such decisions
  - Understanding the difference between "uncertainty" and "risk" is important; *uncertainty ≠ risk*

Terminology: Uncertainty

- Lack of conviction or knowledge especially about an outcome or result
  - Synonyms: Doubt, Skepticism, Suspicion, Mistrust
  - Doubt: suggests both uncertainty and inability to make a decision
  - Skepticism: implies unwillingness to believe without conclusive evidence
  - Suspicion: stresses lack of faith in truth, reality, fairness, or reliability of something or someone
  - Mistrust: genuine doubt based upon suspicion

Merriam-Webster's Collegiate Dictionary, 10th Ed.

Terminology: Risk

- Possibility of loss or injury
- Someone or something that creates or suggests a hazard
- **The chance of loss or the perils to the subject matter of an insurance contract; *also***
  - **the degree of probability of such loss**

Merriam-Webster's Collegiate Dictionary, 10th Ed.

- [Risk - *combination of the probability of occurrence of harm and the severity of that harm* (ISO/IEC Guide 51) and proposed to be adopted by ICH Q9]

Example of a CMC Regulatory Decision: Acceptability of a Post Approval Manufacturing Process Change

- Original NDA or ANDA = CMC Quality & Performance ("Insurance") Contract
  - For example in ANDA's Regulatory commitments = Conditions in executed batch records
- Prior Approval Supplement* (PAS)
  - Product conforms with all established specifications
  - But - "Specifications do not tell the whole story"
    - E.g., Shelf-life and/or bioavailability may have changed and/or a new impurity may be introduced that may not be detected with established analytical methods,…sponsor may not adequately qualify changes (inspection frequency may not be sufficient),….

**prior approval supplement* for process optimization and continuous improvement efforts

Prior Approval Supplement Assessment

- Intended to
  - Ensure adequate qualification of changes (i.e., beyond conformance to specifications)
    - Uncertainty with respect to predictability of accelerated stability test results (e.g., at 3 months) to ensure unchanged shelf-life
      - Also, the time involved in the PAS process forces additional stability data to be gathered
    - Additional dissolution testing
    - Long term stability commitment on post change batches
  - Predominantly reduce uncertainty (also, skepticism and suspicion) since in post approval change scenario risk is generally not quantifiable and is “perceived”

Components of Uncertainty

- Uncertainty arises from inadequate or absence of knowledge
  - Variability (random variation) is often considered to be a component of uncertainty especially in describing analytical measurement uncertainty
- It raises the concern of incorrect decisions
  - Not addressing this concern directly and adequately or erroneously underestimating it in the pretext of risk-based decisions can potentially undermine public trust

Uncertainty Vs. Random Variation

- In decision making there are certain advantage in distinguishing between uncertainty and random variability*
  - Uncertainty forces decision makers to judge/evaluate accuracy of their decisions
    - Example - What to measure/control?
  - Variability forces them to cope with the *certainty* that their decision will have a degree of imprecision
    - Example - How to control?

*National Research Council (NRC) (1994), *Science and Judgment in Risk Assessment.* Washington, DC: National Academy Press.

Understanding the Role of "Uncertainty" and "Risk" in the Current Regulatory System

- One central, and not yet fully resolved, issue is the need for a consensus definition of *pharmaceutical quality* for regulatory purposes
- The scientific challenges facing pharmaceutical manufacturing go well beyond the problem of the clinical readout

(Woodcock 2004)

Understanding the Role of "Uncertainty" and "Risk" in the Current Regulatory System

- Despite the slogan *building quality in*, most quality assessment today relies on end-product testing
- This is a problem in and of itself
- In addition, many of the tests methods currently being used have severe limitations in the modern, mass production environment

(Woodcock, 2004)

NDA Application Approval -FDA's decision on the acceptability of benefit to risk ratio

- Specification limits on quality attributes are often chosen empirically to ensure production of batches that resemble the batches tested in the clinic.
  - However, this approach will only ensure consistent clinical performance if the relationship between those limits and the clinical outcome is understood.
  - Without this understanding, the limits could be overly wide, **unnecessarily tight, or completely irrelevant to clinical performance.**
  - Even worse, other, critically important attributes may not be identified, measured and controlled.

Woodcock, 2004

Predominantly – "uncertainty management" - The foundation for regulatory quality decisions:

- "Quality can not be tested into products; it has to be built in by design" (ICH Q8, Step 2 Document)

Moving towards Risk-Based Definition of Quality (for example, proposed ICH Q8 + Q9)

- Risk is the concept that can connect the desired clinical attributes—clinical performance as labeled, absence of contamination, and availability—to attributes measurable during production.
- *Good pharmaceutical quality* represents an acceptably low risk of failing to achieve the desired clinical attributes
  - link between any measurement and risk?

Woodcock, 2004

An Approach for Quality – Risk Connection

- Concept of *Quality by Design* (QbD)
  - Product and process performance characteristics are **scientifically designed to meet specific objectives**, not merely empirically derived from performance of test batches
  - Characteristics important to desired performance must be derived from a **combination of prior knowledge and experimental assessment during product development**.
  - From this knowledge and data, a **multivariate model linking product and process measurements and desired attributes may be constructed**.
- **Clinical study would then be viewed as confirmatory performance testing of the model**.

Woodcock, 2004

An Approach for Quality – Risk Connection

- A significant challenge
- If we assume pharmacokinetic bioavailability – exposure is an adequate surrogate for safety and efficacy (as we do in many cases)
  - Current approaches for establishing quality – risk connection?
    - Establishing a correlation between *in vitro* drug release and *in vivo* absorption?
    - Understanding of drug absorption mechanism as part of the Biopharmaceutics Classification System?
  - We still do not necessarily connect to risk (since we currently have a procrustean bioequivalence standard of 90% Confidence Interval of 80 -125% for Cmax & AUC) – so, should we then not consider IVIVC and BCS as tools for “uncertainty” management?

Solving Problems Involving Uncertainty

- Points to consider
- Are probabilistic methods and statistical techniques the best available tools?
  - Uncertainty in AI –Fuzzy Sets
  - Probability theory + Fuzzy Logic
  - Bayesian unification may be a way forward

Nozer & Booker 2004

Reducing International "Regulatory Uncertainty"

- Post approval changes or variation requirements differ between US, EU and Japan
- ICH Q8 "Design Space" concept changes the definition of change/variation
- Opportunities to develop more flexible regulatory approaches
  - Risk based decisions
  - Manufacturing process improvement within approved design space without further regulatory review
  - "real time" quality control, leading to reduction of end product testing

There is a limit to which uncertainty can be reduced

- Decisions have to be made under uncertainty
- Therefore, uncertainty has to be managed over the life cycle of a product and its manufacturing facility
  - Controlled
    - Demand management
  - Passive management
    - QbD and demonstrateable “robustness”
  - Active management
    - Creating flexibility – in CMC commitments and facilities Quality System

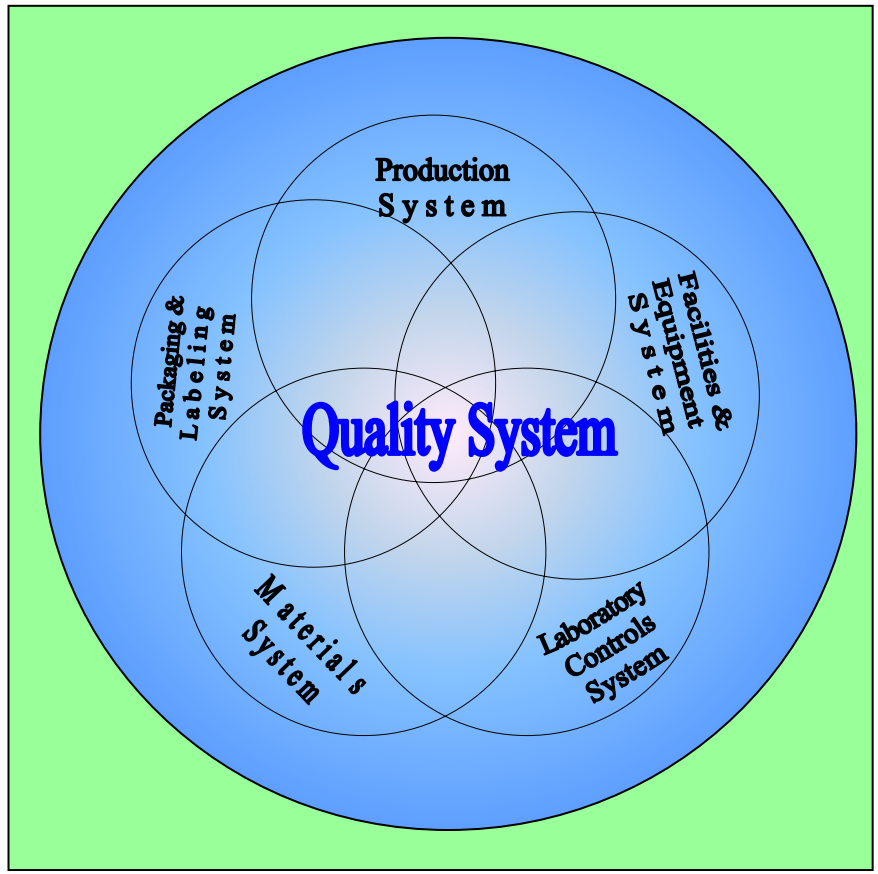
Systems Engineering –to- Engineering a Quality System

Traditional goals

Non-traditional goals
(risk based, flexibility, robustness, scalability, continuous improvement, innovation, efficiency,….)

Characteristics
Complexity, uncertainty

Relationships (between goals & characteristics)
Knowledge and information centric relationships
Fundamental issues



Draft Guidance for Industry
Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations

http://www.fda.gov/cder/guidance/6452dft.doc

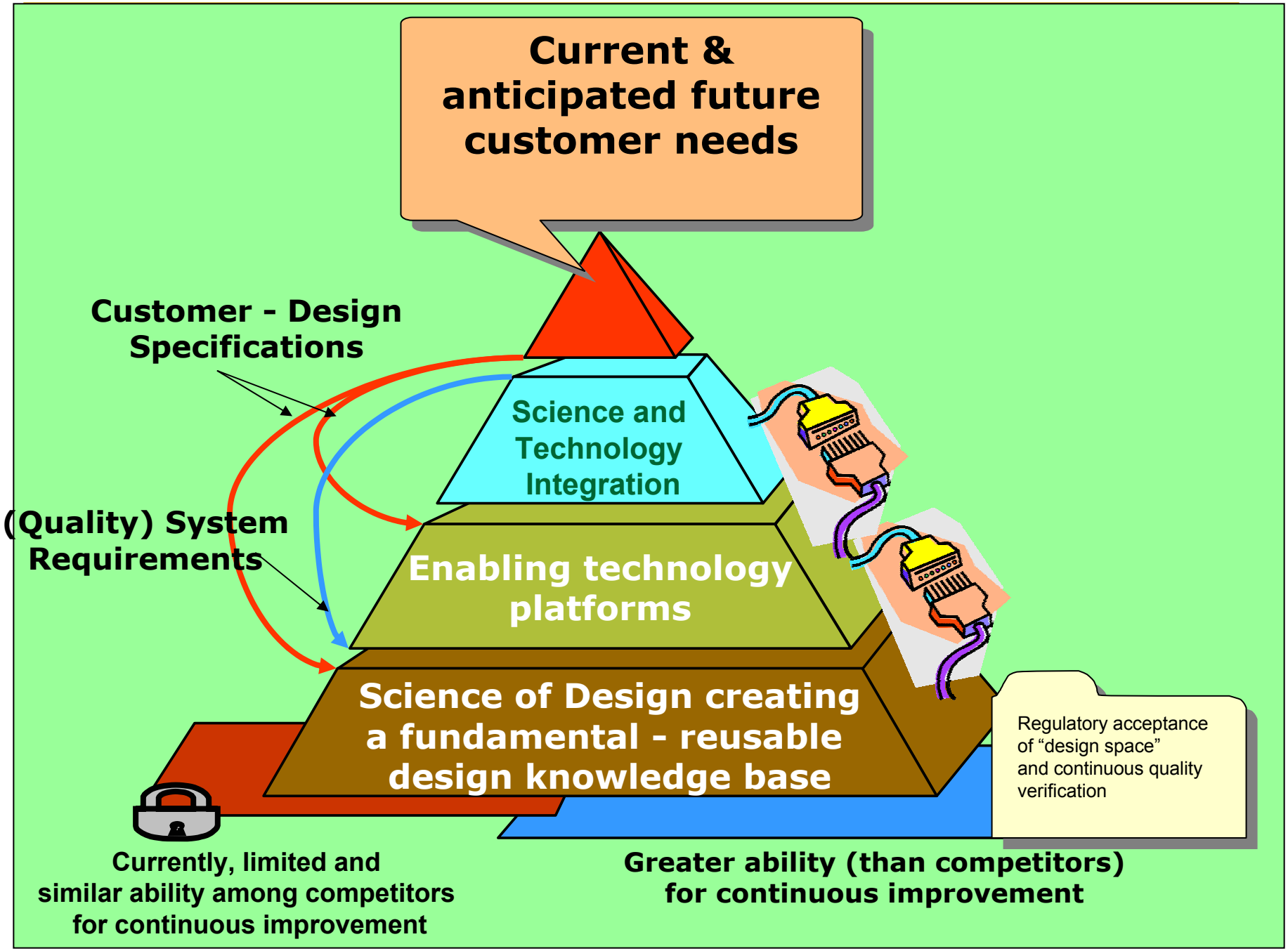
Uncertainty Management*: QbD & Flexibility

Time Scale & Mode of Response	Uncertainty Management	System Modification	
		QbD	Flexibility
Operational	Root cause investigation, Efficiency, etc. – Leaning to R&D	Control of excipients and other sources of "common cause" variability	Reduce CGMP Risk Classification – Continuous Improvement of Quality System
Tactical	On-line control [Design for Manufacturability]	Critical Control Points - Robust process end-point Regulatory Specifications	"Design Space" Real –Time Release, Modular Validation Reg. CMC Approval
Strategic	Science of Design – Design to reduce "Uncertainty"	Sci. & Tech. Integration – Continuous Learning & Improvement Regulatory Communication	Integrate Sci - Enabling Technology Platform – "Plug & Play" "Time to Market" + "Production Efficiency"

* Richard de Neufville. Engineering Systems Symposium, MIT, (2004)

Charting a path forward?

- Understanding current and anticipating future needs of the primary, secondary and tertiary customers
  - Understanding the environment in which these needs have to be fulfilled
- Creating a foundation for “Science of Design”
- Identify, develop or acquire enabling technologies
- Develop a integrated science and technology platform to satisfy customer needs


Current & anticipated future customer needs
Customer - Design Specifications
(Quality) System Requirements
Science and Technology Integration
Enabling technology platforms
Science of Design creating a fundamental - reusable design knowledge base
Regulatory acceptance of "design space" and continuous quality verification
Currently, limited and similar ability among competitors for continuous improvement
Greater ability (than competitors) for continuous improvement

Customer Needs?

- Productivity improvement and higher competition
- Ensure we are ready to meet future needs
  - Increasing complexity (e.g., complex drugs, drug delivery systems, nanotechnology, biotechnology, drug-device – cellular-tissue combinations, etc.) and anticipated need for customization
  - flexible and highly efficient supply chain (e.g., to support genomic based targeted treatment and for customization)
  - a changing global economy, technical talent pool, and complex security needs.

Increasing Complexity increases Uncertainty and in a Risk-averse Regulated System

- Often results in an increase in additional requirements in response to both real and/or perceived inadequacies in risk coverage
- Penalty of non-compliance is significant and can sometimes jeopardize the ability of a non-compliant firm to make independent decisions
- Prioritization of sparse resources for ensuring compliance becomes an ever increasing challenge further increasing the risk of non-compliance
- **In such an environment continuous improvement and innovation is difficult (if not impossible) and productivity is low.**
- **An important societal consequence is that customers have to bear the high cost of inefficiency – increasingly they are not willing or are unable to bear this cost**

Science of Design*

- Often design and development activities are carried out based on experiential knowledge, intuition and rough guidelines – difficult to communicate to individuals from different backgrounds (the “art” argument)
- To achieve and demonstrate Quality by Design, quality of the design (scientific foundation) will need to be effectively communicated
  - individuals from different scientific backgrounds in a company (e.g., quality professionals with background in analytical chemistry)
  - regulators (e.g., CMC reviewers and CGMP investigators)

*http://www.nsf.gov/pubs/2004/nsf04552/nsf04552.htm

Science of Design

- To learn how to represent designs at a much higher level than the current descriptive “recipe” format (e.g., executed batch records, SOP’s) while rigorously documenting key constrains
- Generalize principles and system requirements for managing the interface between knowledge and technology
  - Characteristics of successful designs
- Multidisciplinary communication and collaboration

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