Developing and Regulating Biotechnology Products in a "Risk-Based Environment"

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Highlights

- History of recent regulations and actions
- CGMPs for the 21st Century
- Pharmaceutical Quality System (ICH Q10)
- Pharmaceutical Development / Quality by Design (ICH Q8 & Q8R)
- Quality Risk Management (ICH Q9)
- Concluding thoughts

FDA Recent Regulatory History:

ICH The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (1990 to present)

To achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration.

Q1: Stability (1992)
Q2: Analytical Validation (1993)
Q3: Impurities (1994)
Q5: Quality of Biotechnology Products (1995)
Q6B: Specifications for Biotech and Biological Products (1998)
Q7A: CGMP for Active Pharmaceutical Ingredient (2000)
Q8: Pharmaceutical Development (2004)
Q9: Quality Risk Management (2005)
Q10: Pharmaceutical Quality System (2007)

FDA Recent Regulatory History:

PDUFA The Prescription Drug User Fee Act (PDUFA)

A program under which the pharmaceutical/ biotechnology industry pays certain "user fees" to the Food and Drug Administration (FDA). In exchange for these fees, the FDA agreed, via correspondence with Congress, to a set of performance standards intended to reduce the approval time for New Drug Applications (NDA) and Biological License Applications (BLA).

I (1992)
II (1997)
III (2002)
IV (2007 *Pending)

FDA Recent Regulatory History:

FDAMA FDA Modernization Act of 1997

Includes measures to:

- Modernize the regulation of biological products by bringing them in harmony with the regulations for drugs.
- Eliminate the need for establishment license application.
- Streamline the approval processes for drug and biological manufacturing changes.

FDA Recent Regulatory History:

Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach (August, 2002)

The goals are intended to ensure that:

- The most up-to-date concepts of **risk management** and **quality systems approaches** are incorporated into the manufacture of pharmaceuticals while maintaining product quality
- Manufacturers are encouraged to use the **latest scientific advances** in pharmaceutical manufacturing and technology
- The Agency's submission **review and inspection programs** operate in a coordinated and synergistic manner

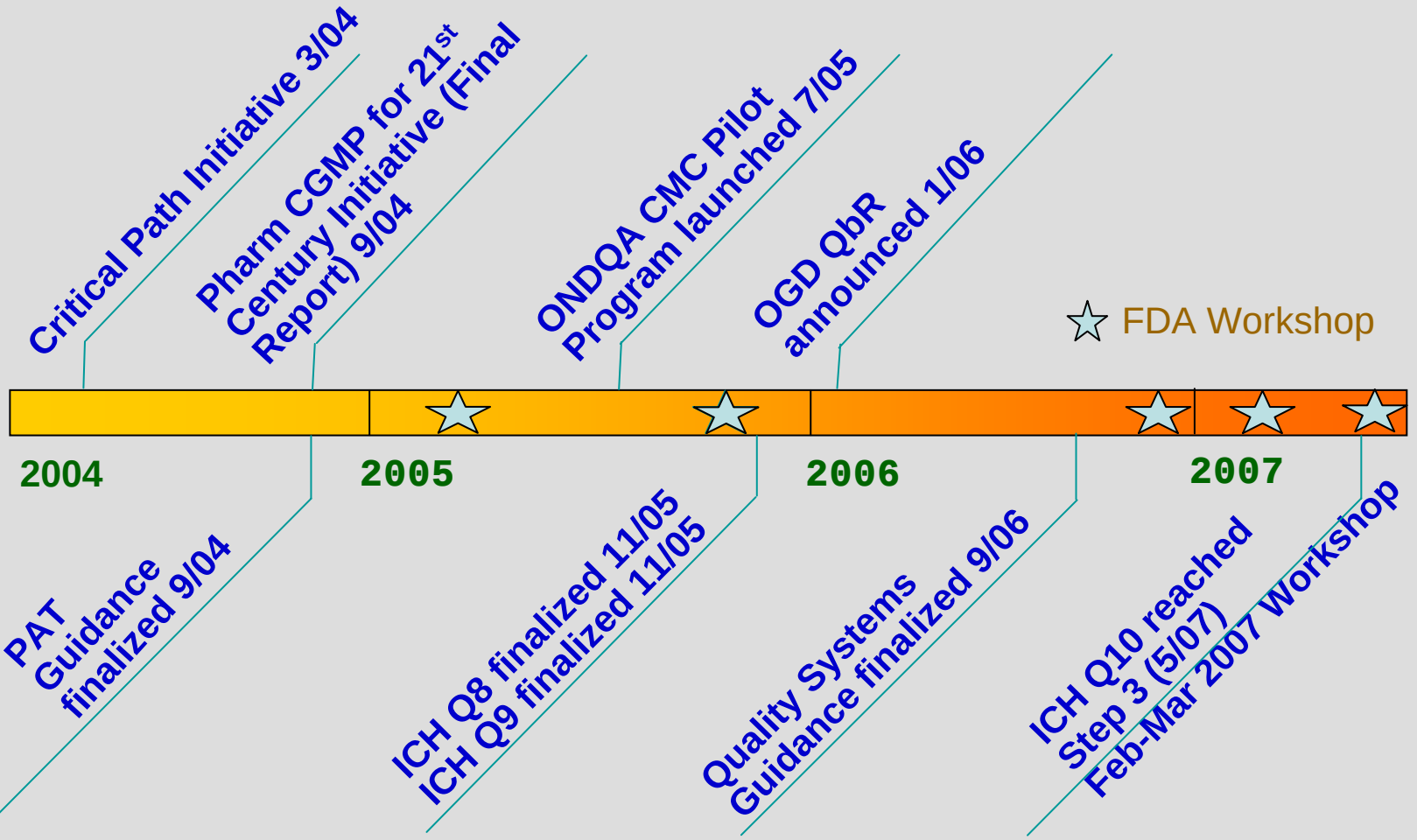
FDA Recent Regulatory History:

Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach (August, 2002) [continued]

The goals are intended to ensure that:

- Regulations and manufacturing **standards are applied consistently** by the Agency and the manufacturer
- Management of the Agency's Risk-Based Approach **encourages innovation** in the pharmaceutical manufacturing sector
- Agency **resources are used effectively and efficiently** to address the most significant health risks

FDA Quality Initiatives: A Timeline



The Desired State: A Mutual Goal of Industry, Society, and the Regulators

Quality

"Good pharmaceutical quality represents an acceptably low risk of failing to achieve the desired clinical attributes."

Quality by Design (QbD)

"Means that product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches."

Janet Woodcock, M.D.
October, 2004

The Desired State: A Mutual Goal of Industry, Society, and the Regulators

"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight".

Janet Woodcock, M.D.
October 5, 2005

FDA Quality in the 21st Century

Knowledge and information exchange are critical to attaining the desired state.

- Medically driven, based on the physician and patient needs.
- Manufacturing driven by understanding of product and process.
- Quality assured by design.

FDA Quality in the 21st Century

Pharmaceutical Quality System (PQS)
ICH Q10

Based on scientific knowledge and an understanding of product and process to

- Enhance the quality and availability of medicines globally to support public health
- Develop and utilize effective monitoring and control systems for process performance and product quality.
- Facilitate appropriate, innovation and continuous improvement throughout the product lifecycle

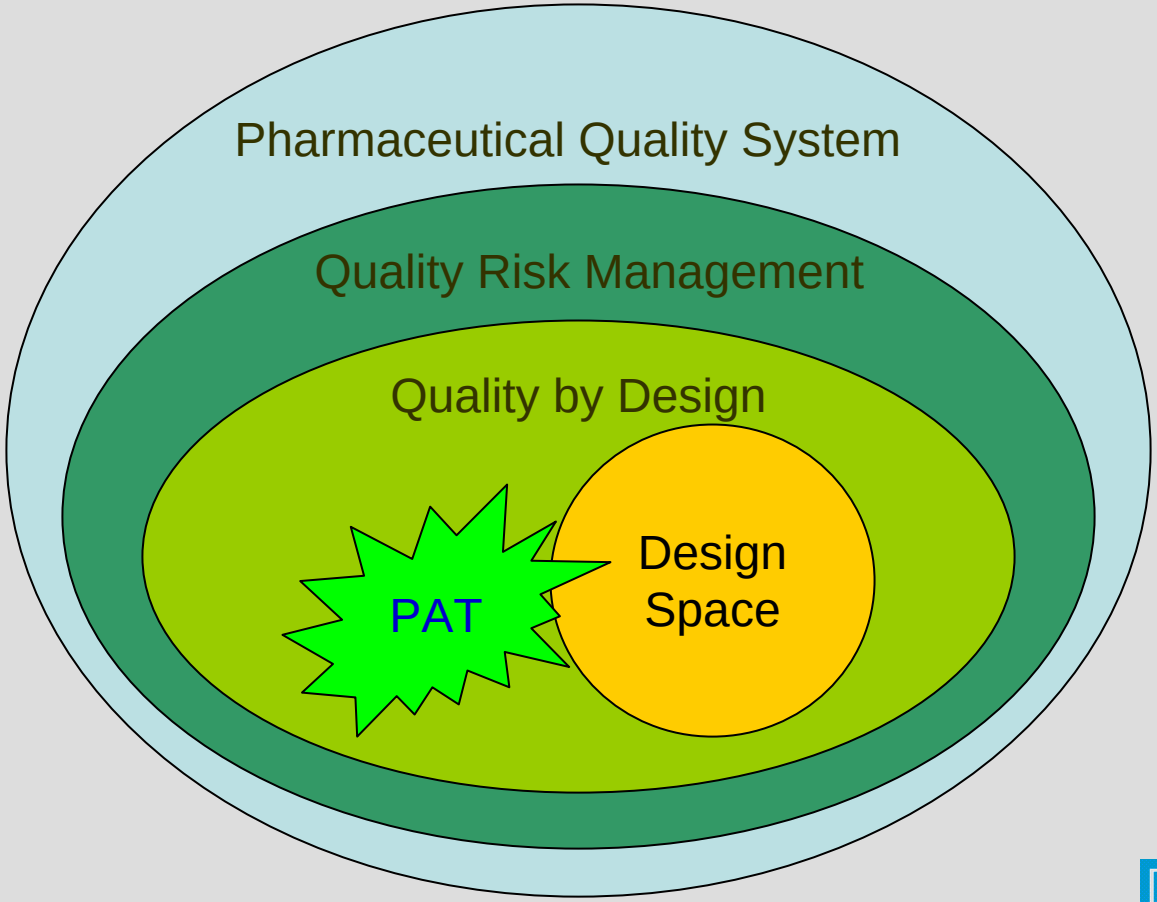
FDA Quality in the 21st Century

Pharmaceutical Quality System (PQS)
ICH Q10

- Process understanding links manufacturing controls to Critical Quality Attributes/specifications and hence to the desired performance of the drug product
- In the desired state, quality control is moved upstream to critical process steps and Critical process parameters rather than relying on end-product testing; reporting of these values in the COA is important
- To achieve this desired state, relevant design information is necessary for quality assessment

FDA Quality in the 21st Century

Pharmaceutical Quality System (PQS)



FDA Quality in the 21st Century

Process Analytical Technology (PAT)

A system for **designing**, **analyzing**, and **controlling** manufacturing through **timely measurements** (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality.

FDA Quality in the 21st Century

Process Analytical Technology

- Product quality and performance achieved and assured by **design of effective and efficient manufacturing processes**.
- **Risk-based regulatory scrutiny** that relates to the level of understanding of how formulation and manufacturing process factors affect product quality and performance and the capability of process control strategies to prevent or mitigate risk of producing a poor quality product.
- **Continuous "real time" assurance of quality**.
- Regulatory policies and procedures tailored to recognize the **level of scientific knowledge** supporting product applications, process validation, and process capability.

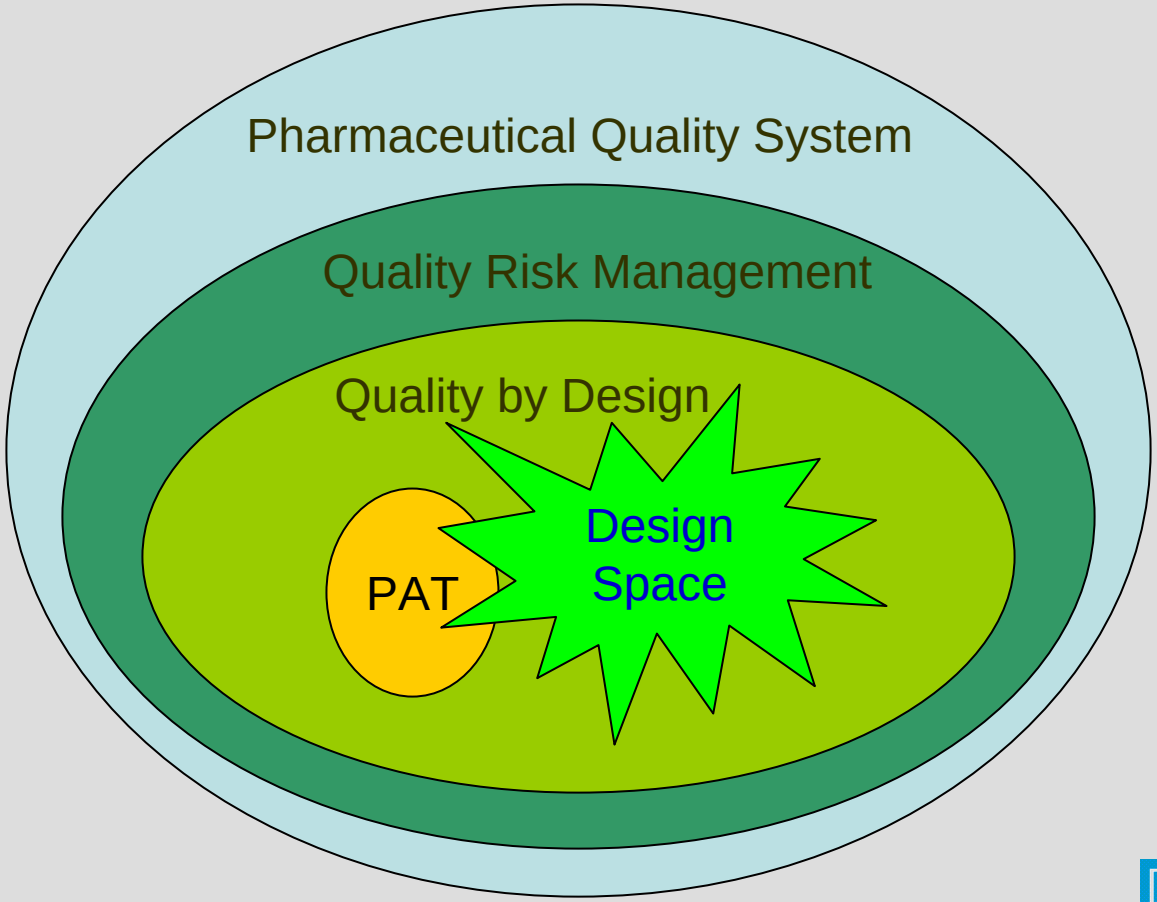
FDA Quality in the 21st Century

Process Analytical Technology

A desired goal of PAT is to design and develop well understood processes that will consistently ensure a predefined quality at the end of the manufacturing process. Such procedures would be consistent with the basic tenet of quality by design and could reduce risks to quality and regulatory concerns while improving efficiency.

FDA Quality in the 21st Century

Pharmaceutical Quality System (PQS)



FDA Quality in the 21st Century

From ICH Q8 …

"The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The **information and knowledge gained from pharmaceutical development studies and manufacturing experience** provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls".

FDA Quality in the 21st Century

ICH Q8 – Design Space Concept

The ***multidimensional combination and interaction*** of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality

Traditional one dimensional process range doesn't meet Q8 definition and will not lead to "regulatory flexibility"

FDA Quality in the 21st Century

ICH Q8 – Design Space Determination

- First-principles approach
  - combination of experimental data and mechanistic knowledge of chemistry, physics, and engineering to ***model and predict performance***
    - ***Desirable but not required or expected in every case***
- Statistically designed experiments (DOEs)
  - efficient method for determining ***impact of multiple parameters and their interactions***
- Scale-up correlations
  - a semi-empirical approach to translate operating conditions
  - between different scales or pieces of equipment

M. Nasr, FDA

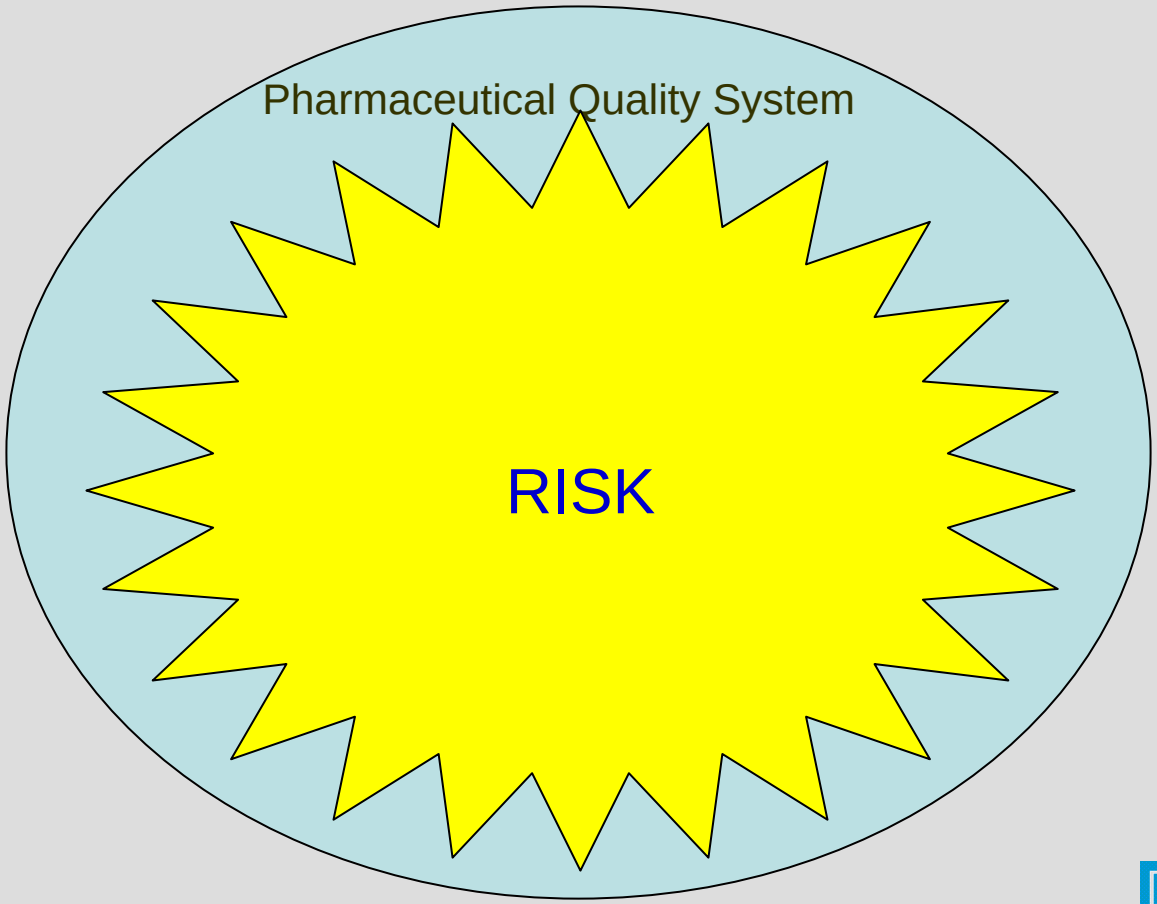
FDA View on QbD

Quality by Design is:

- Scientific, risk-based, holistic and proactive approach to pharmaceutical development
- Deliberate design effort from product conception through commercialization
- Full understanding of how product attributes and process relate to product performance

FDA Quality in the 21st Century

Pharmaceutical Quality System (PQS)



Risk-Based Quality Assessment

Risk is defined as the **combination** of the probability of occurrence of ***harm*** and the ***severity*** of that harm.

- The evaluation of the risk to quality should be based on **scientific knowledge** and ultimately link to the **protection of the patient**
- The level of effort, formality and documentation of the quality risk management process should be **commensurate with the level of risk**.

Risk-Based Quality Assessment

Risk assessment consists of the **identification** of hazards and the **analysis** and **evaluation** of risks associated with exposure to those hazards

Factors to consider when assessing risk

- Product Availability
- Target Patient Population
- Acceptable Level of Risk
- Probability and Severity of Hazard
- Dosage Form

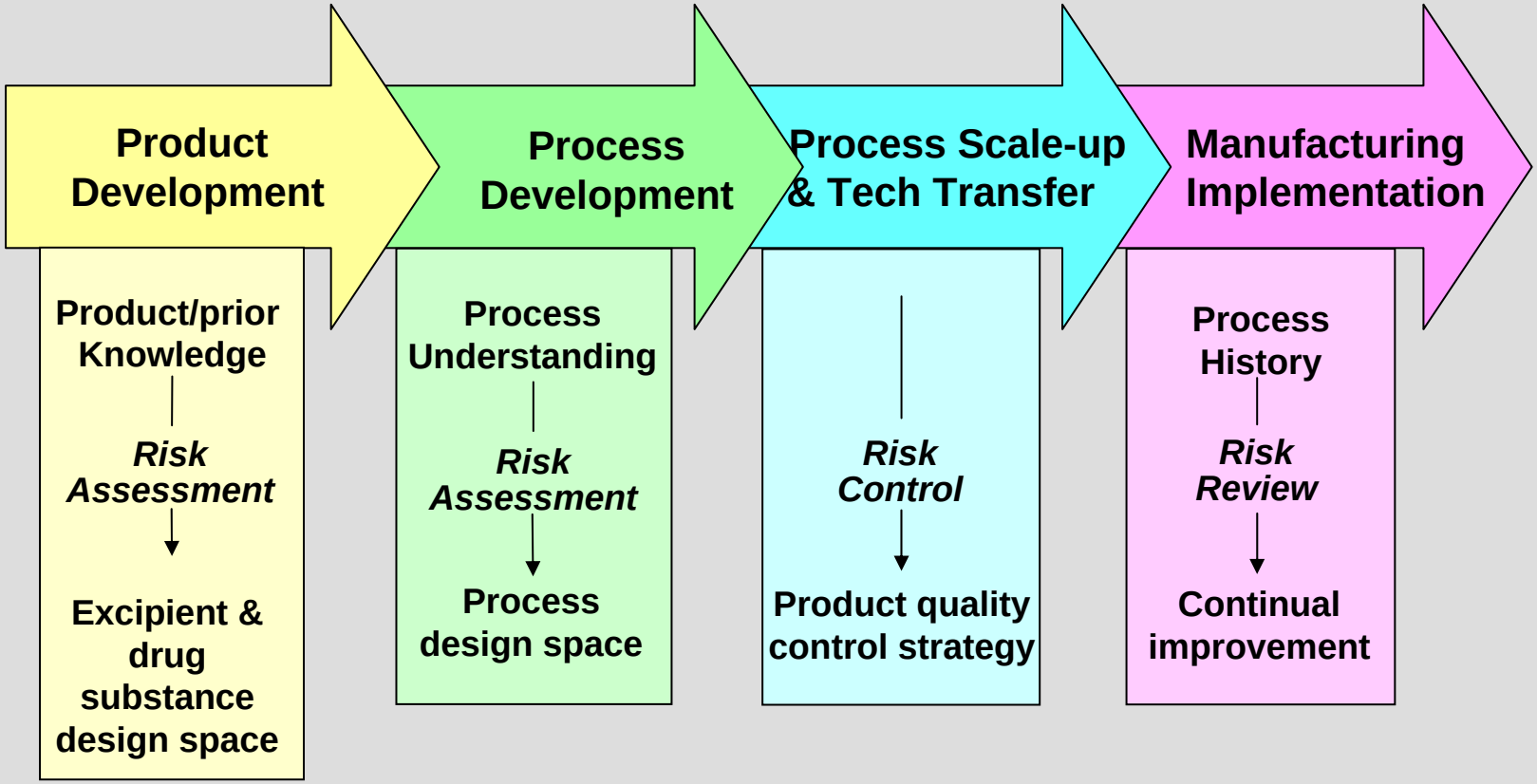
- Product Development Knowledge
- Quality systems
- Process Step

Risk-Based Quality Assessment

Quality risk management should include systematic processes designed to **coordinate, facilitate and improve science-based decision making** with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following:

- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk;
- Assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk assessment;
- Identify a leader and necessary resources;
- Specify a timeline, deliverables and appropriate level of decision making for the risk management process.

Role of Quality Risk Management in Development & Manufacturing



M. Nasr, FDA

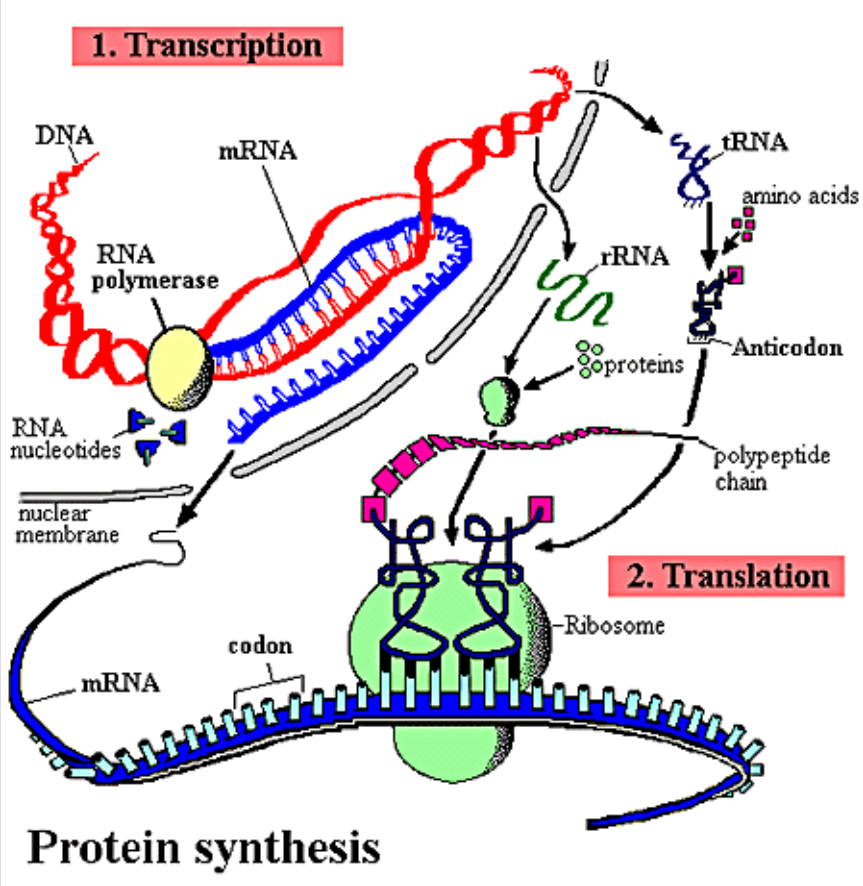
FDA Quality in the 21st Century

Benefits of a Risk-Based System

- Improved patient **safety** and drug **availability**
- Sharing of robust product and process **knowledge** between Industry and FDA
- Reasonable, continual process **improvement** within specified design space
- Enhanced product **quality** assurance

Know your process

Look to Nature for Quality by Design



Thanks

Grateful for discussions and ideas from my colleagues in
Office of New Drug Quality Assessment, CDER

namely, John Hill, Su Tran, Chi-wan Chen,

particularly, Moheb Nasr.