QbD –Quality by Design

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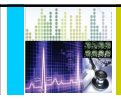
Motivation



Integration of prior knowledge and pharmaceutical development into CMC submission and review

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 (Am Pharm Rev, 2004)

What is QbD?

- The application of formal risk assessment, risk management and risk mitigation techniques to the manufacture and control of drugs
- A systematic approach to development that begins with predefined objectives. It emphasizes product and process understanding and process control
- Based on sound science and quality risk management
- An on-going process

QbD Fundamental

"It is important to recognize that quality cannot be tested into products, i.e., quality should be built in by design."

(ICH8)

QbD benefits

- Getting at the right process knowledge => Value to manufacturers, FDA and patients (Kelly Canter, 2006)
- Have a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight (Janet Woodcock, 2005)
- Create a harmonized pharmaceutical quality **system** applicable across the **life cycle** of the product emphasizing an **integrated** approach to ***quality risk* management and science** (Moheb M. Nasr, 2007)

QbD significance

- QbD means designing and developing formulations and manufacturing processes to ensure a predefined quality
- QbD requires understanding how formulation and manufacturing process variables influence product quality
- QbD ensures product quality with effective control strategy *(along with ICH Q9 and Q10)*

(Lawrence X. Yu, FDA)

Flexibility

- Working within the design space is not considered as a change.
- Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.

(ICH8)

ICH guidelines

- Q8 (R2) – Pharmaceutical Development
- Q9 – Quality Risk Management
- Q10 – Pharmaceutical Quality System

Critical attributes (ICH Q8)

- **Critical Quality Attribute (CQA):** A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.
- **Critical Process Parameter (CPP):** A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.
- **Critical Material Attribute (CMA):** A physical, chemical, biological or microbiological property or characteristic of a material that should be within an appropriate limit, range, or distribution to ensure the desired quality.

Terminology

- **Control Strategy:** A planned set of controls, derived from current product and process understanding that ensures process performance and product quality.
- **Design Space:** The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.
- **Proven Acceptable Range (PAR):** A characterized range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria.

Terminology

- **Quality Target Product Profile (QTPP):** A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.

How to achieve QbD objectives

- Product and process 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.

Janet Woodcock (Am Pharm Rev, 2004)

How to achieve QbD objectives

The final link between the product and the customer-driven quality attributes is the quality system for manufacturing.

Ideally, the quality system reflects and addresses

- customer requirements
- ensures integration of product and process knowledge gained during development
- ensures ongoing control of manufacturing processes, and
- enables continuous improvement

Janet Woodcock (Am Pharm Rev, 2004)

Approaches to Pharmaceutical Development

Aspects	Traditional	QbD
Pharmaceutical development	Empirical; typically univariate experiments	Systematic; multivariate experiments
Manufacturing process	Fixed; validation on 3 initial full-scale batches; focus on reproducibility	Adjustable within design space; continuous verification within design space; focus on control strategy and robustness
Process control	In-process testing for go/no-go; offline analysis w/slow response	PAT utilized for feedback and feed forward at real time
Product specification	Primary means of quality control; based on batch data	Part of the overall quality control strategy; based on desired product performance
Control strategy	Mainly by intermediate and end-product testing	Risk-based; controls shifted upstream; real-time release
Lifecycle management	Reactive to problems & OOS; post-approval changes needed	Continual improvement enabled within design space

The QbD process

Safety and Efficacy

Define Quality Target Product Profile

Design Product and Process

Identify Critical Quality Attributes

Identify Critical Process Parameters

Control Strategy

The QbD cycle

Product knowledge

Process understanding

Moheb Nasr (2005)

QbD tools

- Design of Experiments (DOE)
- Risk assessment tools:
  - Failure Mode and Effect Analysis (FMEA)
  - Risk assessment spreadsheets
  - Ishikawa ("fishbone") analysis
- Process Analytical Technology (PAT)

The Design Space

- Multi-dimensional space that encompasses combinations of product design, manufacturing process design, manufacturing process parameters and raw material quality that provide assurance of suitable quality and performance

$$\text{Design Space} = \{x \mid P(Y \in A \mid X = x) \geq 1-\alpha\}$$

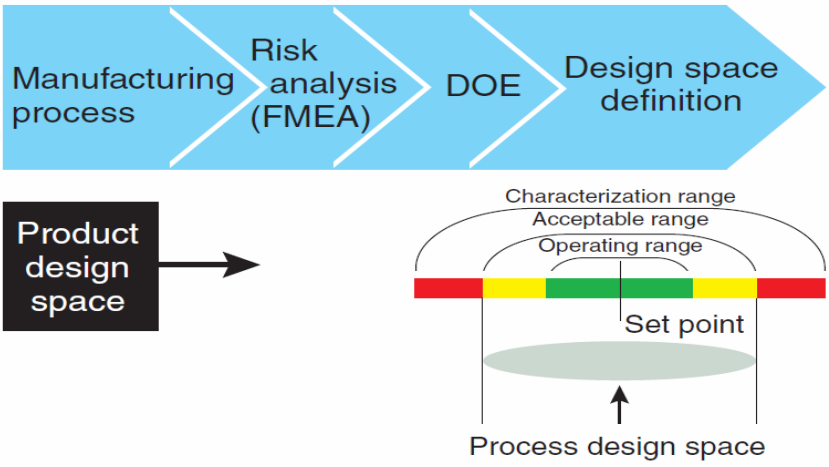
- The Design Space is simply the set of all *reliable* recipes
- The Design Space **is not** the set of all recipes whose results **on average** (across batches) meet product specifications

Process understanding

A process is well understood when:

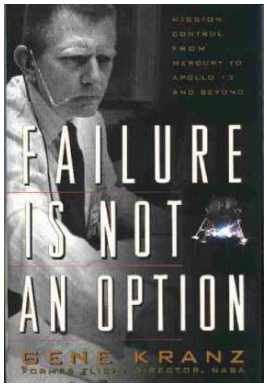
- All critical sources of variability are identified and explained;
- Variability is managed by the process; and,
- Product quality attributes can be accurately and reliably predicted over the design space

The creation of process design space



Rathore & Winkle (Nature Biotechnology, 2009)

FMEA Failure Mode and Effects Analysis



- FMEA is a risk-assessment tool that was developed after the end of WW-II in the US military
- The first large project to use FMEA was NASA's Apollo space mission to the Moon, with the idea of "making it right the first time"
- During the late 70's and 80's, FMEA was adopted by Ford Motor Company and others American automotive industry (AIAG). From there it penetrated into the electronics, plastic & other industries, which supply to the automotive industry

FMEA methodology

- FMEA starts to be applied in the pharmaceutical industry as a tool for risk assessment and risk mitigation
- With a few changes, the FDA adopted Ford's format of FMEA
- FMEA is basically a brainstorming process of mapping all potential causes of failures in a system / a product / an activity with the intension to identify sources of risk
- An important supplement to FMEA is a Control Plan or Control Strategy

FMEA methodology

- In FMEA three questions are asked:
  - What could go wrong (**Failure Mode**)
  - What would be the effect of the failure, assuming that it actually happened (**Severity**)
  - What is the chance to detect the failure after it occurred (**Detectability**)
- Each of the three inputs gets a score, usually from 1 to 5 or 1 to 10

FMEA methodology

- A Risk Priority Number (RPN) is calculated from multiplying the three scores
- The list of RPNs is sorted in a Pareto way
- Some threshold may be set for RPNs to decide which issues are the most critical ones and should result corrective actions
- Knowledge gaps may be covered with experimentation such as DOE

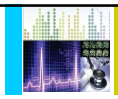
FMEA benefits

- Discovers **potential** (up front) single-point failures
- Leverages process understanding and sets a light on gaps in knowledge
- Increases the probability of meeting the schedule for product launch
- Increases the probability of product success
- Mitigating risk

Keys to success

- Use standard ranking for failure probability, severity and detectability.
- Enforce consistent terminology
- Use FMEA outputs for decision support
- Ensure action items from FMEA are pursued to completion
- Establish a library of FMEA best practices
- FMEA documents are living documents. They should be visited and updated periodically

Limitations and abuse



- Frequently, human errors and hostile environments are overlooked
- Because the technique examines individual faults taken singly (Single-Point-Faults – SPF), the combined effects of coexisting failures may not be considered
- For complex processes / systems the FMEA process can be extraordinarily tedious and time consuming
- Failure probabilities can be hard to obtain
- RPN “adjusted” to obtain lower values