Design of Experiment (DoE) in Pharmaceutical Research

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ACKNOWLEDGEMENTS

My Sincere
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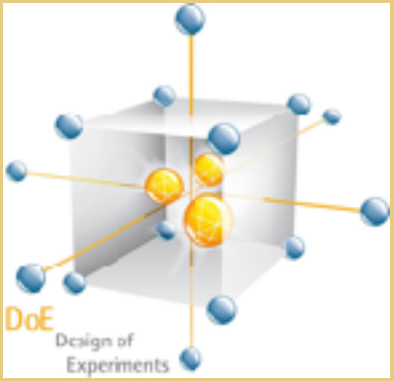


Central APTI Team

Design of Experiments

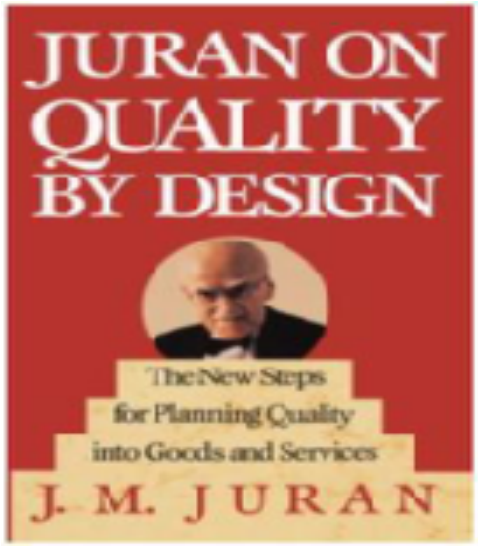
1. Basics
2. Case study - Two Designs
   (FD, FFD and CCD)

Design of Experiments

- What is DoE?
- Why to Use DoE?
- When to Use DoE?
- How to Use DoE?
- Qbd and DoE?

THE QUALITY MANTRA

"Quality can not be tested into products; it has to be built in by design"



Joseph M Juran

What is Quality by Design (QbD) ?

- *Systematic approach*
- *Predefined objectives*
- *product and process understanding*
- *Quality risk management*

Step 1 - Categorization of Drug Properties

TPP → QTPP → RA-1 → CQAs → MA & PPs → RA-2 → DoE → CMAs & CPPs → Desig n space → Control strateg y → RA-3

Step 1 | Step 2 | Step 3 | Step 4 | Step 5

Target Product Profile (TPP) is patient and labelling centred concept:

- **Mechanism of action**
  The mechanism of the product to produces an effect on a living organism.
- **Clinical pharmacology**
  Pharmacokinetic information, distribution and pathways for transformation.
- **Indication for use**
  Target disease or manifestation of a disease and/or population.
- **Primary efficacy endpoints**
  The most important clinical outcome measure.
- **Secondary efficacy endpoints**
  Additional criteria to be met during a clinical trial (not required to obtain a successful positive clinical trial result).

Step 1 - Categorization of Drug Properties

Quality Target Product Profile (QTPP)

- a quantitative surrogate for aspects of clinical safety and efficacy
- for designing and optimizing a formulation and manufacturing process, (includes quantitative targets) :

- Indication and route of administration
- Dosage form and strength
- Container closure system
- Attributes affecting pharmacokinetic characteristics
- Drug product quality criteria

Step 2 - Risk Assessment 1: Identification of CQAs from QTPPs

Initial Risk Assessment (RA-1)

- to shortlists the QTPPs - that are critical for the patients.

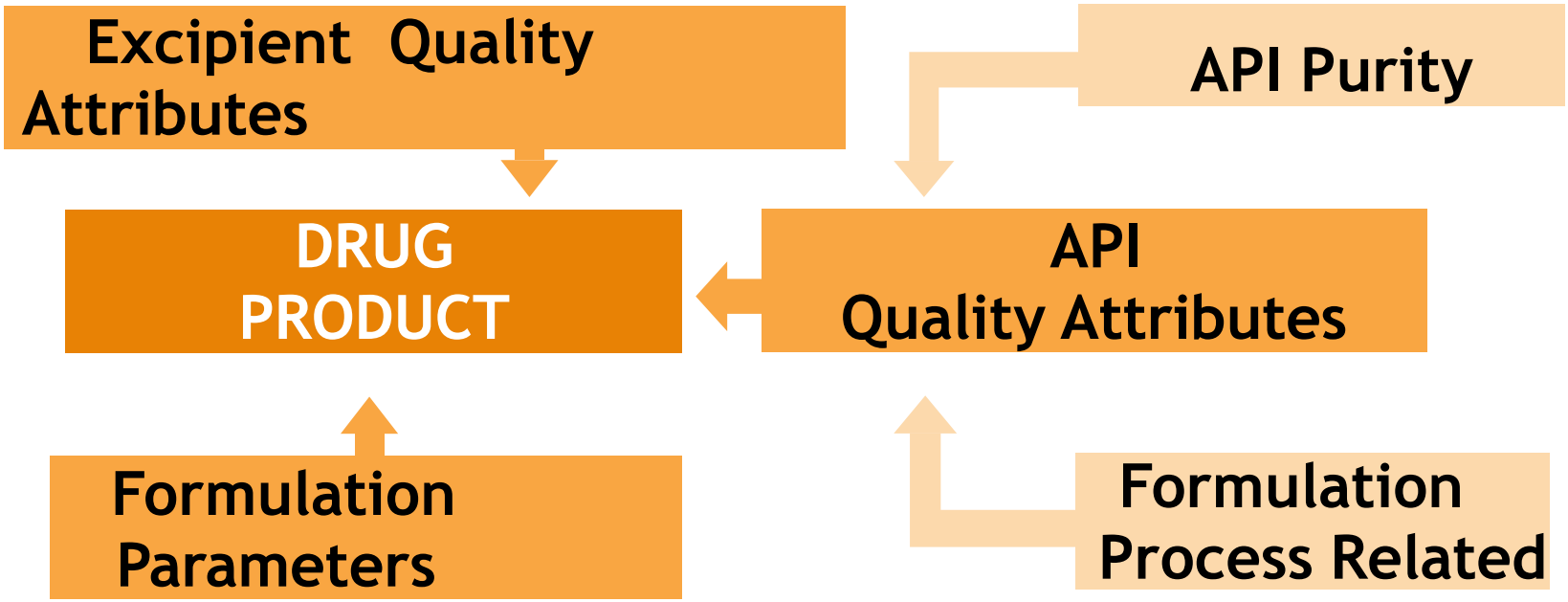
- **QTPPs**
  - Sterility
  - Colour
  - Stability
  - Drug Release
  - Dissolution
  - Odour
  - Particle size

→ **CQAs**

Step 2 - Risk Assessment 1: Identification of CQAs from QTPPs

Critical Quality Attributes (CQAs)

(within an appropriate limit or distribution to ensure the desired quality).



Step 3 - Risk Assessment 2: Identification of PPs and MAs

Material Attribute (MA)

(any physical, chemical, biological or microbiological property of materials) e.g.

Purity | Porosity | Moisture level | Specific volume | Sterility

Process Parameter (PP)

(any input operating parameter of a process) e.g.:

Mixing speed | Flow rate | Temperature | Pressure

Step 3 - Risk Assessment 2: Identification of PPs and MAs

Risk Assessment after development (RA-2)

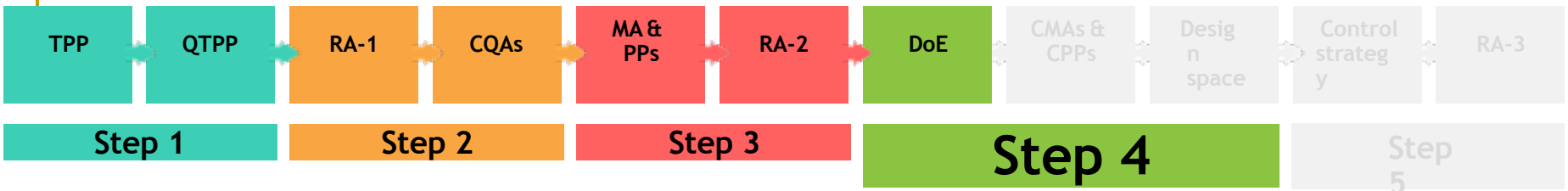
(performed to identify the important input variables for the DoE).

MAs & PPs

Temperature
Moisture level
Mixing speed
Porosity
Pressure

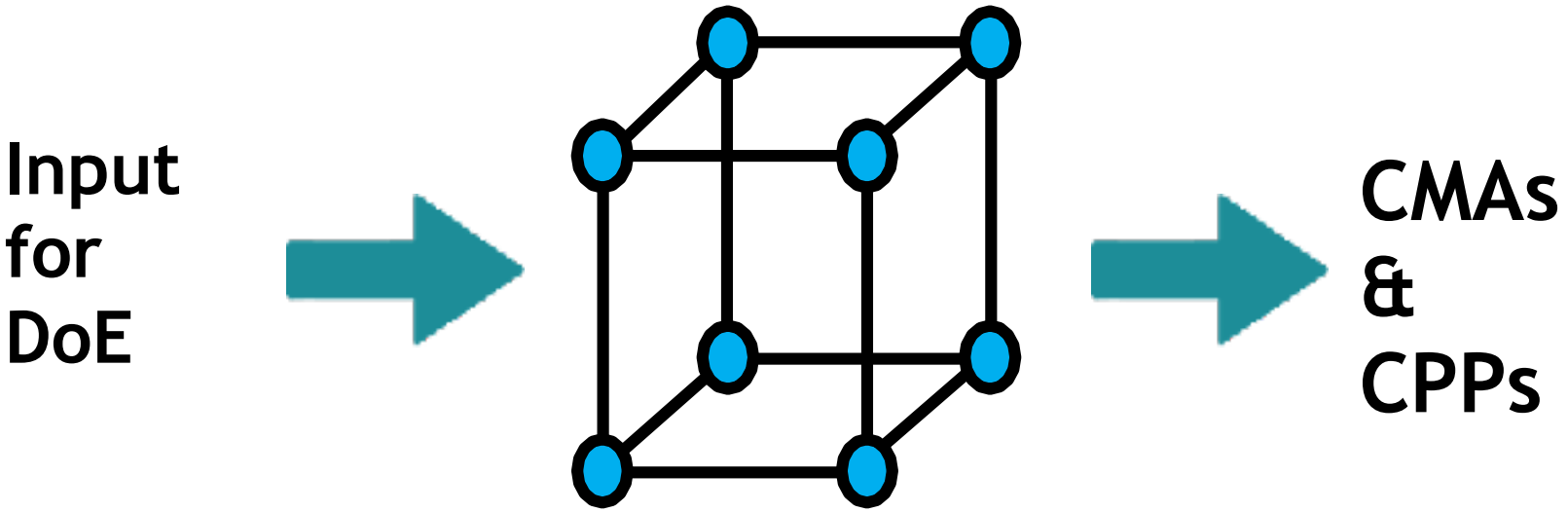
Input for DoE

Step 4 - Optimization of the Effects of the Input Variables on the CQAs

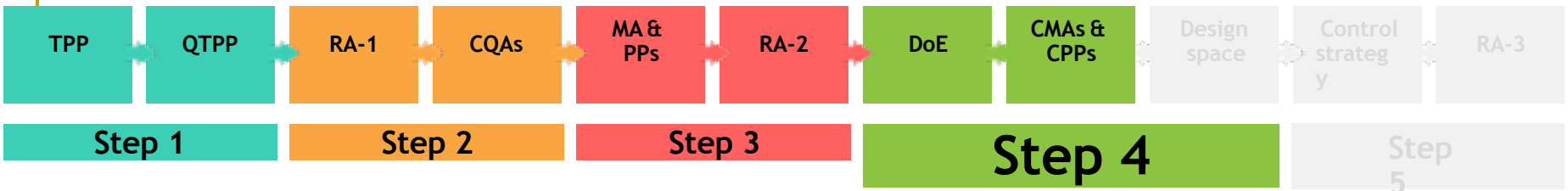


Design of Experiments (DoE)

(output of the DoE is the set of variables that affect the CQAs significantly).



Step 4 - Optimization of the Effects of the Input Variables on the CQAs



Critical Material Attributes (CMAs)

(MAs that need to be controlled to ensure the desired quality)

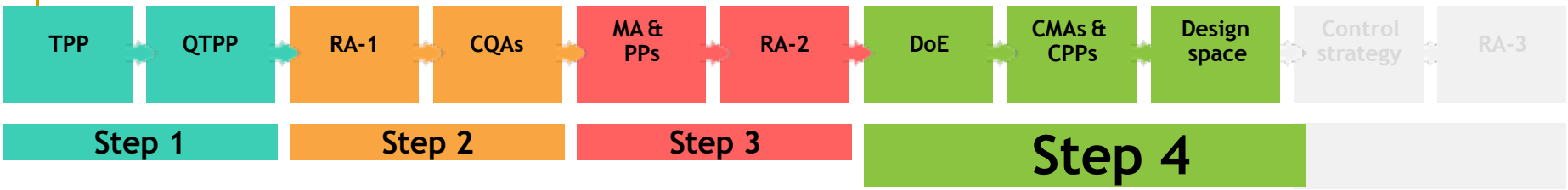
CMAs are independent of each other - (i.e. Particle Size and Purity)

Critical Process Parameters (CPPs)

(PPs that can
cause the product to fail to meet the desired quality).

Temperature	Cooling rate	Rotation speed	Agitation	Feed type and rate	pH

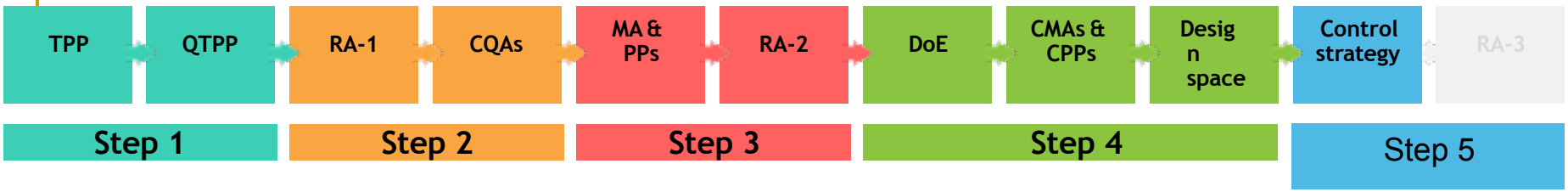
Step 4 - Optimization of the Effects of the Input Variables on the CQAs



Design Space (ICH Q8)

(Multidimensional combination and interaction of MAs and PPs demonstrated to provide assurance of quality)

Step 5 - Control Strategy and Risk Control



Control Strategy (ICH Q10)

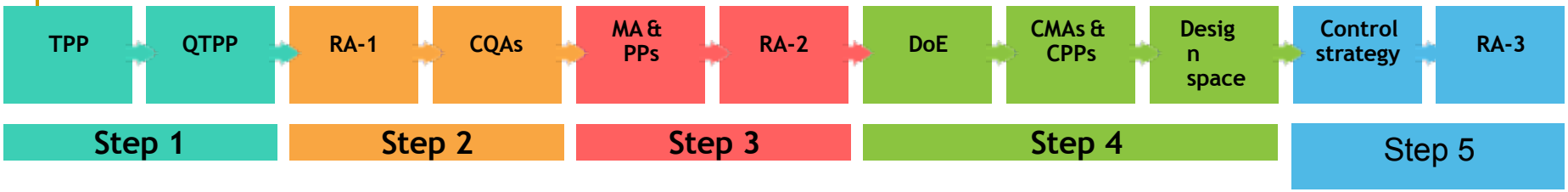
(planned set of controls derived from current product and process understanding - assures process performance and product quality.

Elements of a control strategy can include:

- Identification and qualification of raw materials
- Quantitative determination of active ingredients in finished products
- Quantitative discrimination of physiochemical parameters in finished products
- In-process control of physiochemical parameters

PAT

Step 5 - Control Strategy and Risk Control

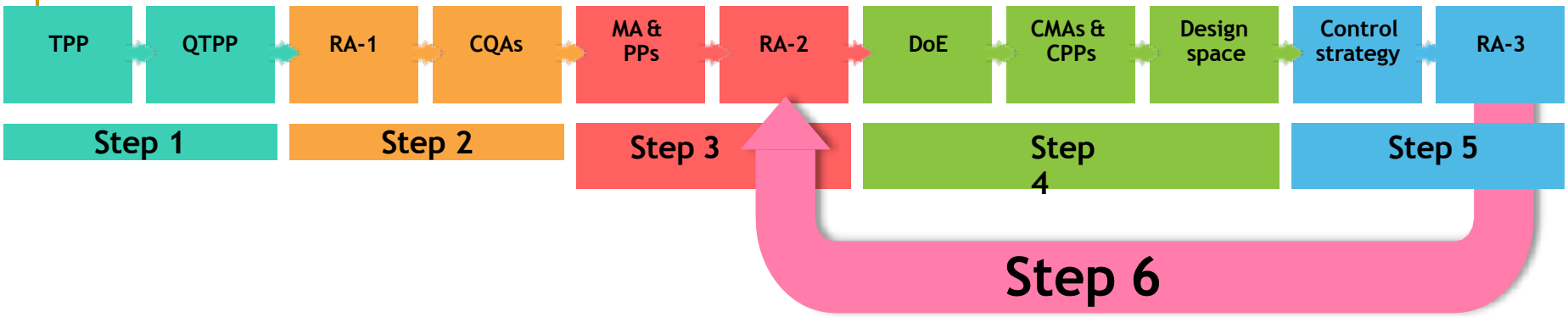


Risk Assessment after implementation of control strategy (RA-3) -

CQAs is re-evaluated to determine whether it has been reduced after optimization with respect to the risk that existed during RA-2.

- Quality Attribute Criticality
- Process Capability
- Testing Strategy
- Quality Risk Mgmt.

Step 6 - Feedback for continuous improvement

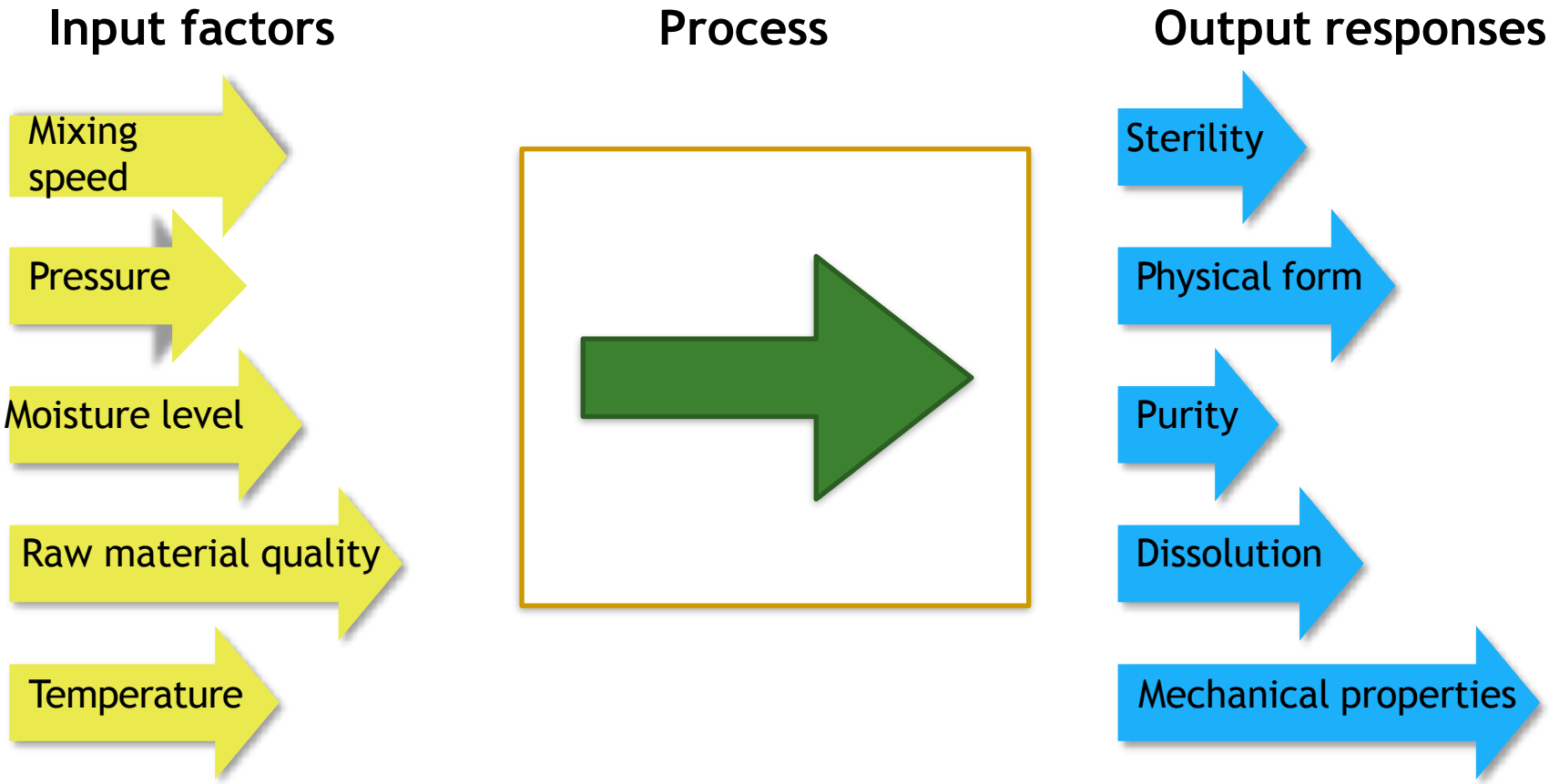


Feedback for continuous improvement

Japanese productivity philosophy known as Kaizen.

What is Design of Experiments?

The properties of products and processes are affected by many factors:



What is Design of Experiments?

Design **o**f **E**xperiments (DoE) is a process to organize the experiments to answer the questions of interest clearly and efficiently.

"Design of Experiment
(*optimize)*

simply means to make as

Perfect, Effective, or Functional

as possible.

DOE: Why to use it ?

- To get to market faster
- For competitive advantage in business
- To increase return on investment
- To produce highest quality product

Evolution of DOE …

- Trial and error method
  - Depends on one's knowledge and experience
  - Depends on one's luck

- One factor at a time
  - Does not examine all permutations and combinations
  - Can not examine interactions

- Design of experiments
  - Can predict the results of experiments not yet performed
  - Can predict the best conditions to meet multiple goals

The strategy for setting up experiments to obtain information efficiently and precisely is called

EXPERIMENTAL DESIGN.

Apart from experimental strategy, it also includes

DATA ANALYSIS

resulting from the experiments.

The experimental designs originated from the work of SIR RONALD FISCHER and PROF. FRANK YATES

The Design of Experiments

ENSURES

FORMULATION QUALITY,

SAVES TIME,

LABOR

and MONEY.

DOE: When to use it ?

- Screening experiments
  - Select the key factors (CMAs and CPPs) that influence the response
- Modeling experiments
  - Maximize or minimize response
  - Characterize and optimize response

DOE: How to use it ?

- VARIABLE / FACTOR:
  - *Independent Variables*
  - *Dependent Variables*

Independent Variables

Independent variables

- Quantitative
- Qualitative

Quantitative variables

--- Numeric values and continuous.

e.g. Time, Temperature, Amount of polymer, Plasticizer, Superdisintegrants etc.

such as 1%, 2%, 3% concentration

QUALITATIVE VARIABLES

Qualitative Variables :

(also known as *categorical variables*)

e.g. Type of polymer, component or machine.

DEPENDENT VARIABLES

Characteristics of the finished drug product are *Dependent Variables*

Or

Response Variables.

e.g. Drug release profile, Percent drug entrapment, Pellet size distribution, Moisture uptake etc.

LEVELS

The Values or designation assigned to a factor.

-1 = lowest factor levels

0 = intermediate (central level)

+1 = highest factor levels

CODING

Coding involves the
Orthogonality Of Effects
and depicts effects and interaction (s).

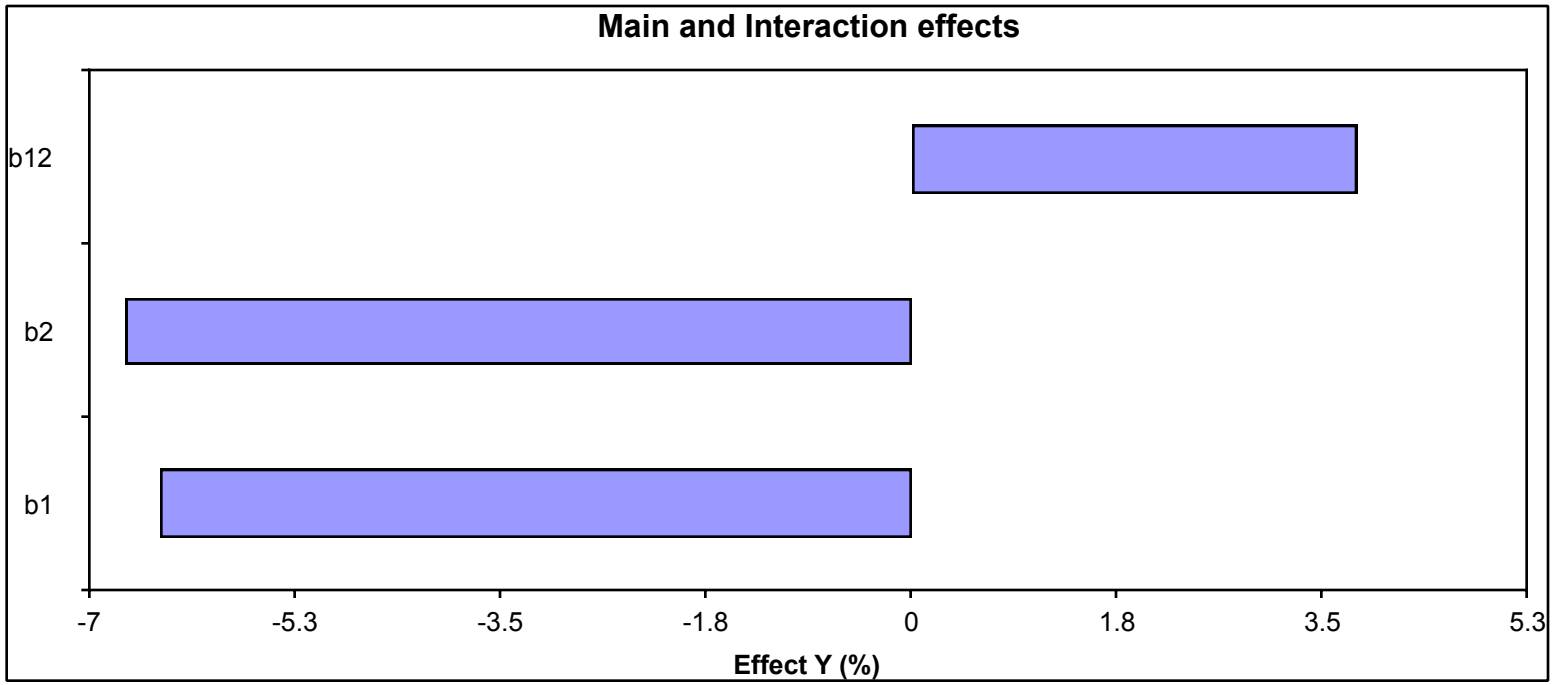
It allows not only easier calculation of coefficients and coefficient variances, but easier depiction of response surfaces as well.

ORTHOGONALITY

Conversely, lack of orthogonality (or independence) is termed *confounding* or *aliasing.*

EFFECT PLOT

Effects plot is plotted between the magnitude of various coefficients for the effects and/or interactions against the response variable.



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EXPERIMENTAL DOMAIN

The dimensional space defined by the coded variables is known

FACTOR SPACE.

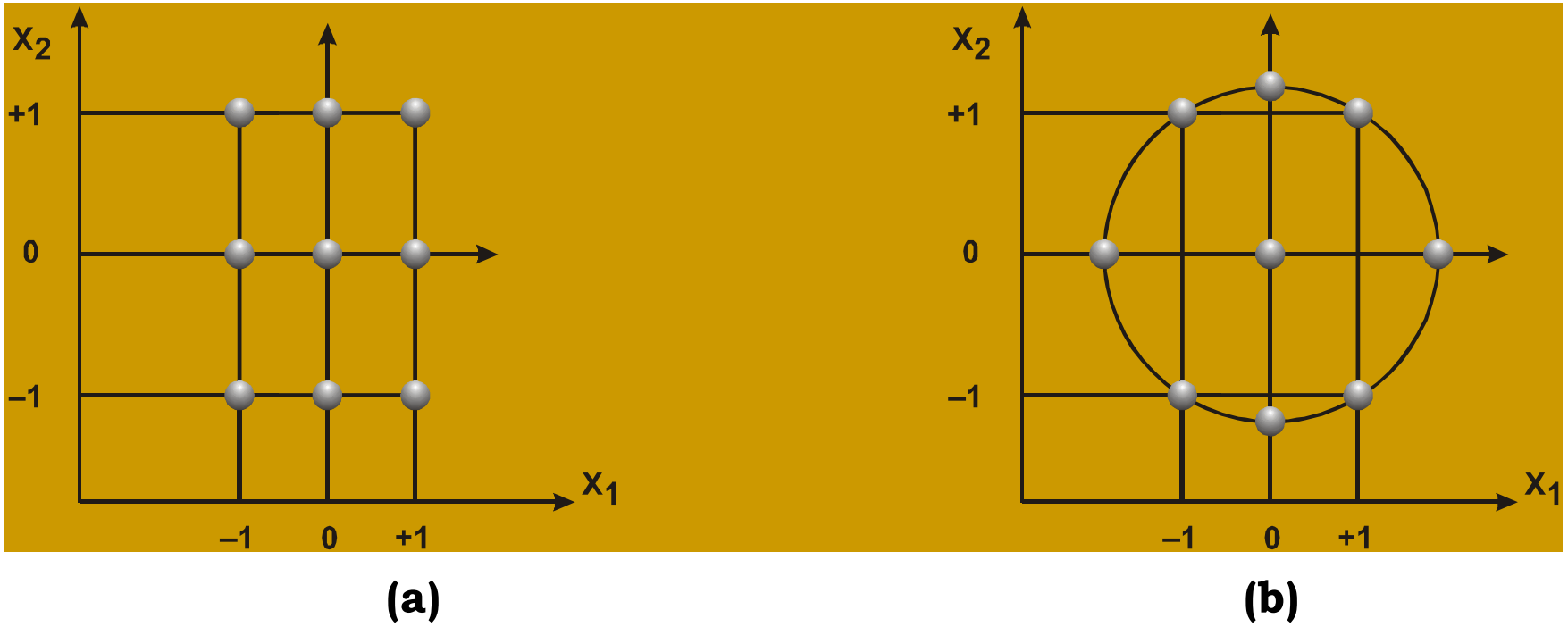
The part of the factor space, investigated experimentally for optimization, is the

Experimental domain.

OR

Region of interest,

Domain in a Central Composite Design (CCD)



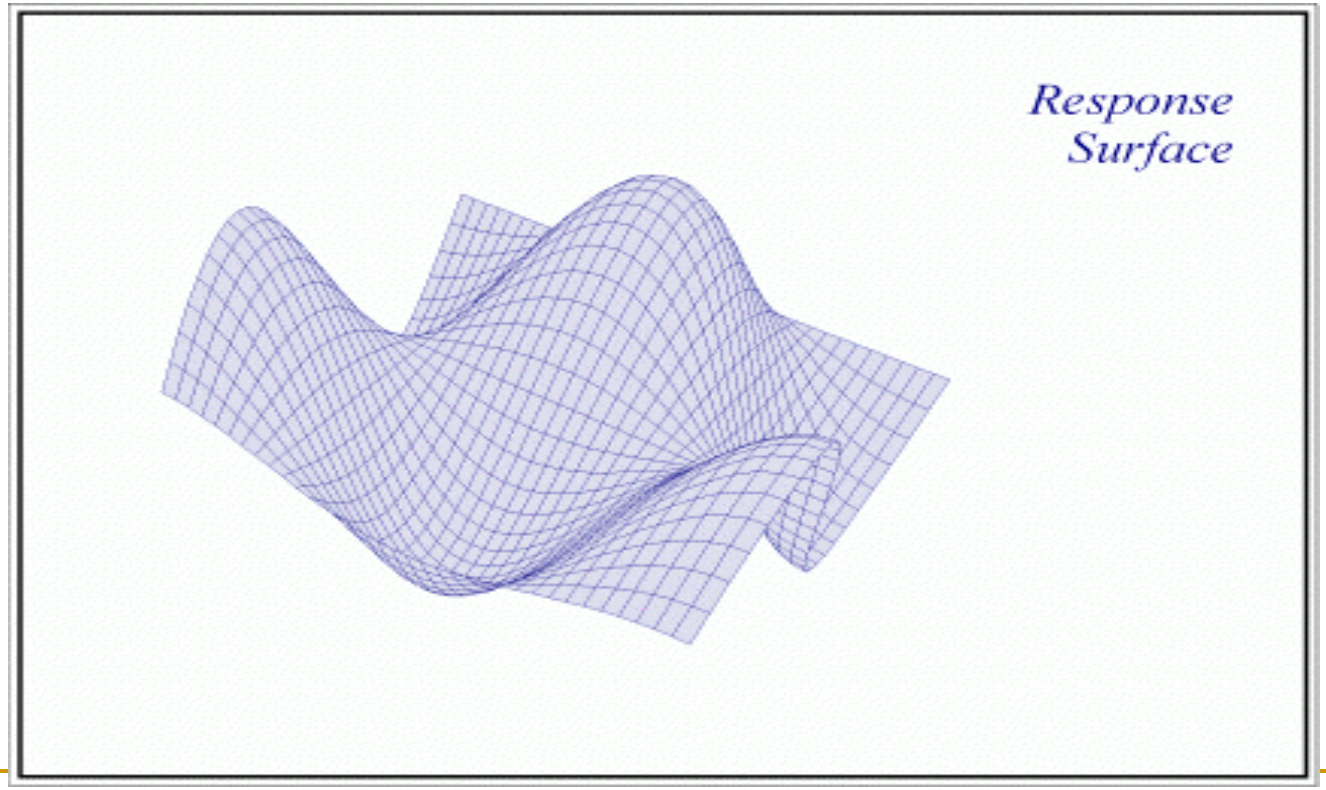
Diagrammatic representation of central composite design (a) rectangular domain with α=1; (b) spherical domain with α = 1.414

RESPONSE SURFACE

The response surface can be visual representation of relationship between measured responses and *independent variables*.

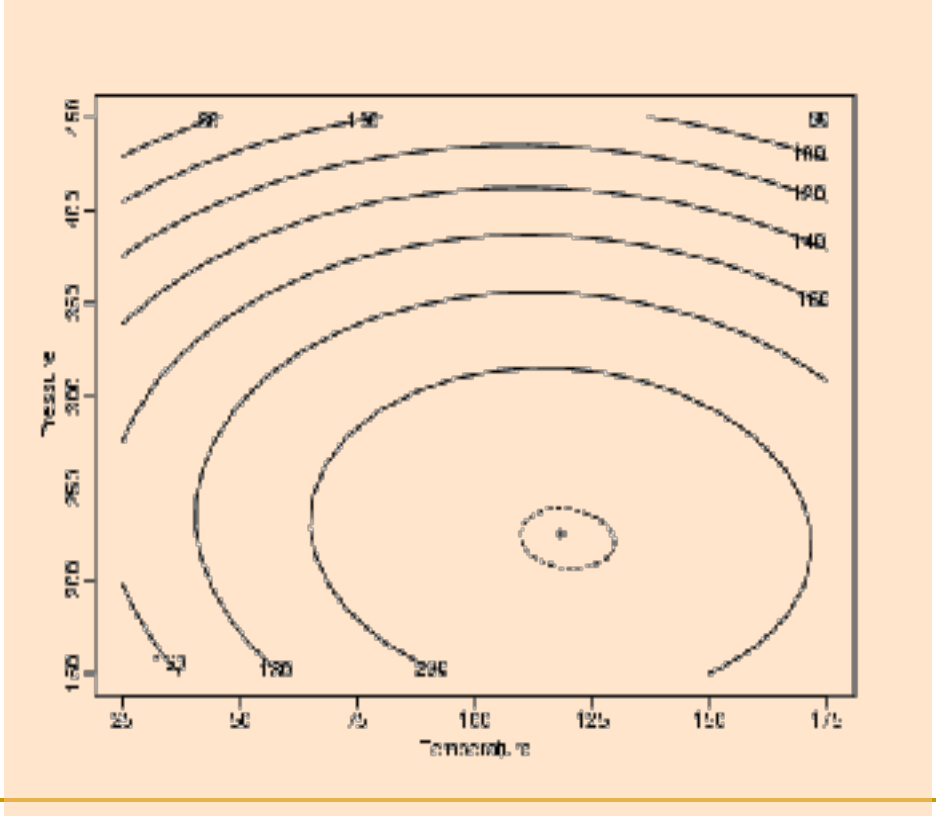
RESPONSE SURFACE PLOT

3-D graphical representation of a response variable plotted against two independent variables.



CONTOUR PLOT

2D-graph between one independent variable versus another holding magnitude of response and other variables constant



How To Use DOE ?

- **PLAN**
  - ✓ Form a hypothesis and create an experimental design
- **DO**
  - ✓ Test the hypothesis
- **CHECK**
  - ✓ Verify the replicability of the experiment
- **ACT**
  - ✓ Make the proven hypothesis a part of standard

PROCESS IN "DOE"

List all possible process and response variables (both qualitative and quantitative)

PROCESS IN "DOE"

Select the ranges and levels for each variable

PROCESS IN "DOE"

Decide on the orthogonal experiments, schedule for randomization, transformation of data and number of replicates

PROCESS IN "DOE"

Perform quick screening experiments and identify critical variables

PROCESS IN "DOE"

Collect extensive experimental data with respect to all critical variables

PROCESS IN "DOE"

Use statistical methods (ANOVA) to distinguish between error and results

- Linear model or
- Non-linear model

A mathematical model is used to map the response

Process in DOE

Mathematical Model:

- Predicting the main effects
- Identifying significant variables
- Predicting the interactions

MATHEMATICAL MODEL

Model (for 2^n factorial design) represented by a polynomial equation:

$$Y = \beta_0 + \sum_{i=1}^{n} \beta_i x_i + \sum_{i=1}^{n} \sum_{j=i+1}^{n} \beta_{ij} x_i x_j + \sum_{i=1}^{n} \sum_{j=i+1}^{n} \sum_{k=j+1}^{n} \beta_{ijk} x_i x_j x_k$$

Where, Y is response, β_0 is a constant, β_i represent the coefficients of main effects, β_{ij}, β_{ijk} represent the coefficients of first-order and second-order interactions and x_i represents a set of variables.

MATHEMATICAL MODEL

- Explain the relationship and arrangement of experiments in factor space.
- Quality of experimental design depends on the mathematical model

Tomorrow Work

Insight to Multi Linear regression and ANOVA - before case study

(Factorial Design and Central Composite Design)