ACSTM
Asian Conference on Science, Technology & Medicine

Title:
Addressing the Framework for Quality by Design in Nanotechnology Delivery Systems

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Pharmaceutical Product Development
The Desired State

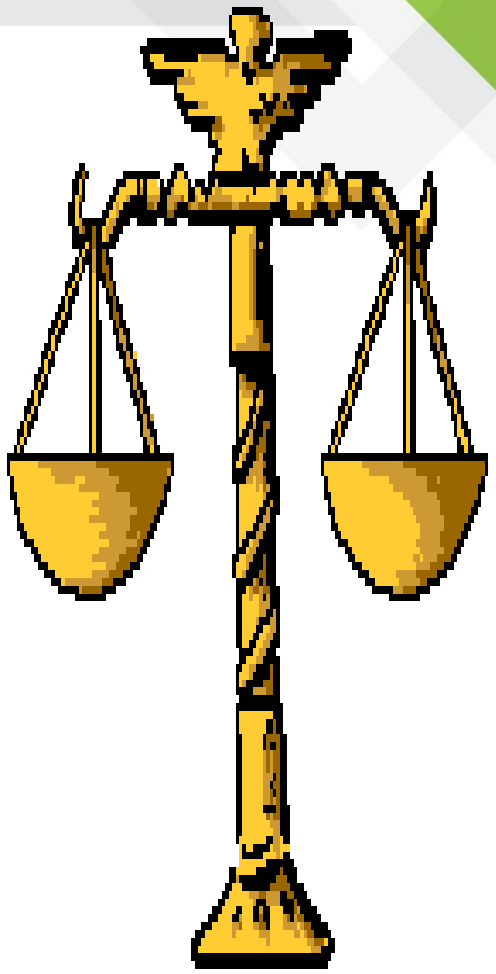
A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight

…Janet Woodcock, 2013
Director, Center for Drug Evaluation and Research, FDA

Web Source: https://qbdworks.com/dr-janet-woodcock-cder-fda-ispe2013/

A Drug Delivery System

A Drug Delivery System is usually an Intricate Device (Complicated) that, apart from the API, involves a Plethora of Excipients, e.g., Release Controlling Polymers, Surfactants, Lipids, Emulgent, Suspending agents, Processes, etc., where each one Contributes towards the Drug Delivery Performance in its Own Characteristic Manner.



At times during day-today life, it is not that easy to take optimal decisions….

Everyday, Everyone

confronts different situations…

has diverse duties to perform…

different persons to please…

with dissimilar needs, demands & tastes…

has myriad options to choose from…

The ultimate aim has always been to be balanced, happy and contended…

At times during day-today life, it is not that easy to take optimal decisions….

But How???...

Only by choosing
a few vital among them
and
Optimizing their use rationally…

Hence….

"Optimization" is the key to keep things in the balanced and orderly manner

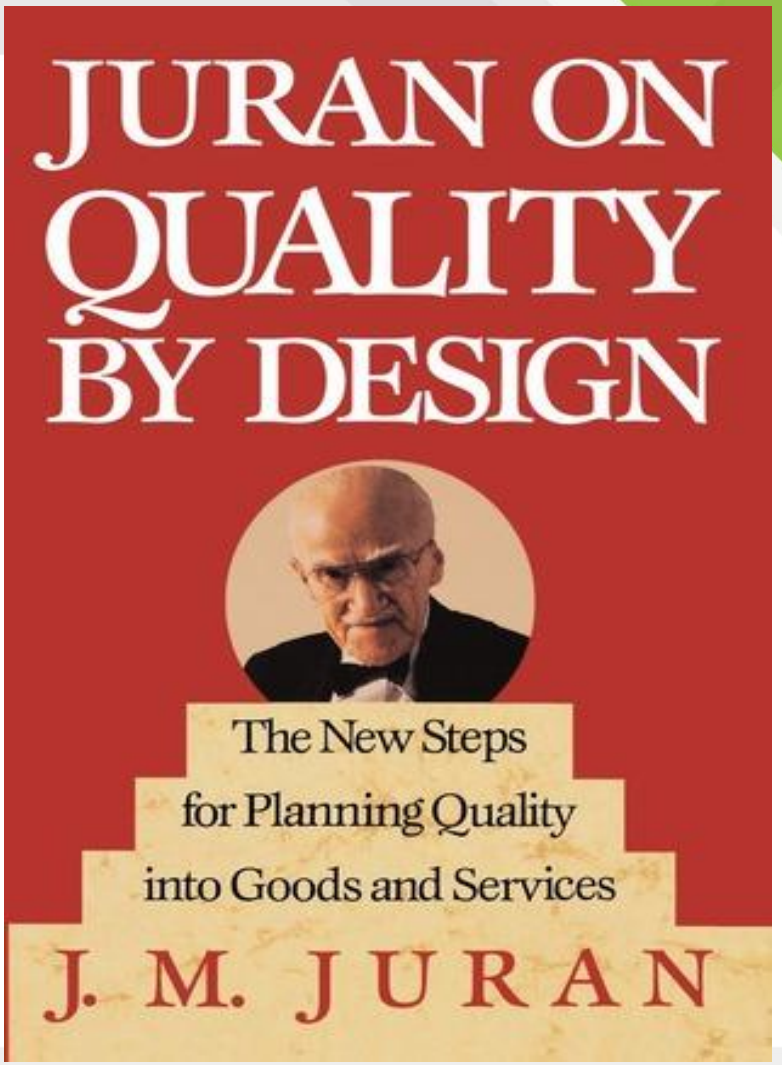
Systematic Optimization using Design of Experiments (DoE)

…is a rational approach that enables teams to learn about product/process behaviour by running a series of experiments, where maximum amount of information is learned using minimum number of studies.

Quality by Design (QbD): The Concept

From the Horse's Mouth

- *QbD concept was first outlined by J.M. Juran, a celebrated quality expert.*
- *He proposed that the "Quality" could be planned in the first place to avoid quality crisis by building "Quality" into the product.*



QbD
What is New in It?

- *QbD is a culture encompassing quality principles and strong compliance to it.*
- *QbD refocuses attention and resources on what is important to the customer, e.g., the patients, health professionals, distribution chain, etc.*
- *QbD incorporates elements of risk assessment & management.*

QbD: The Ultimate Objectives

To Design and Develop Drug Products with the Desired Attributes of/ with a team to simultaneously design and develop products that have:

Quality Excellence

Customer Satisfaction

Ease of Production

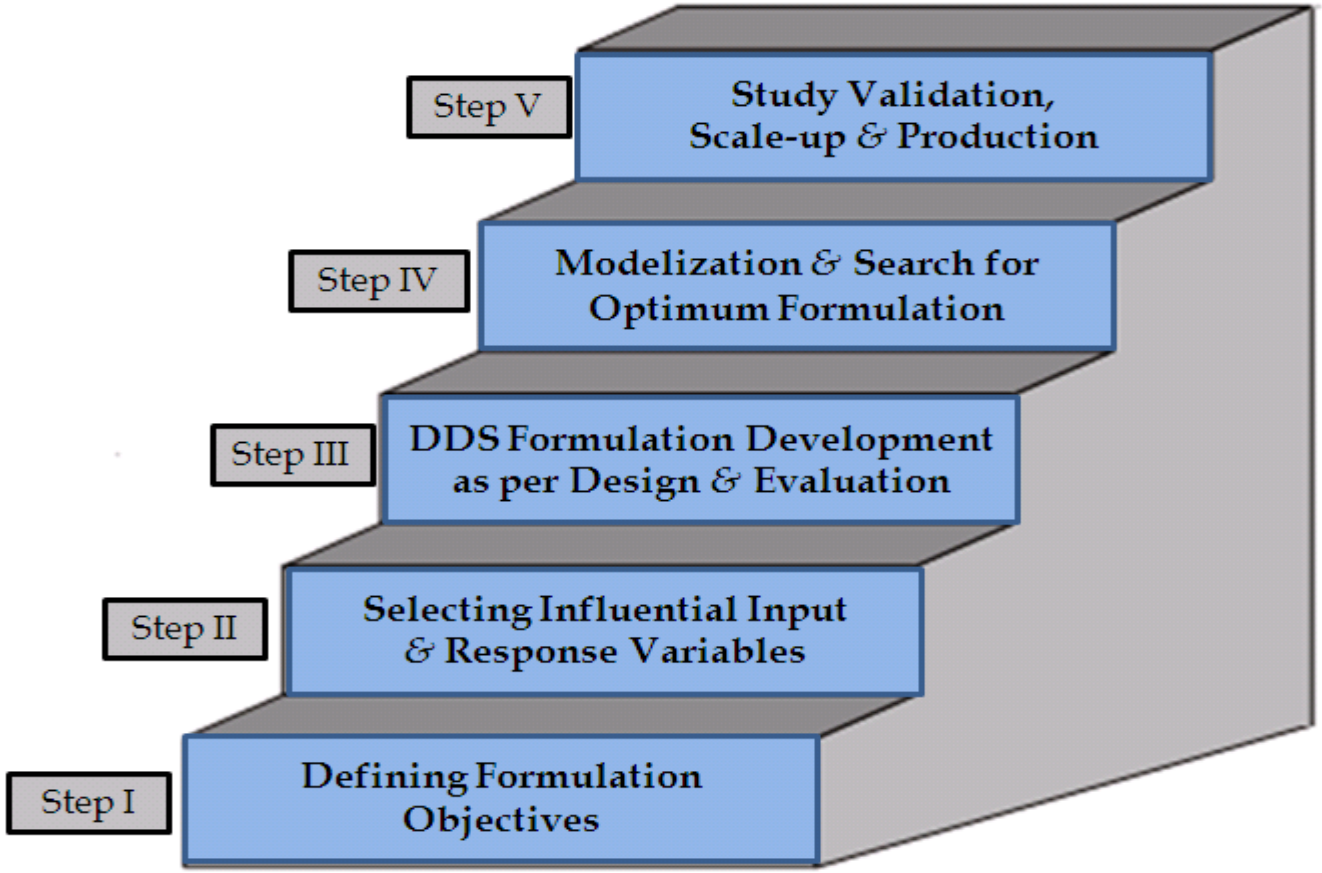
QbD
Why to Implement It?

Resources are much more critical today than they ever were in the past…

- ***Time***
- ***Money***
- ***Effort***
- ***Enhanced Knowledge Sharing***
- ***Improve Time to Market/Consumer Generic Skepticism***
- ***Reduced Cost Associated with Poor Quality (Recalls & Rejects)***
- ***Improve Minimize the Post-Approval Changes***

- Less Rework/Less Wastage of Materials/Less Risk of Failure
- Fewer Design Changes
- Shorter Lead Times
- Quicker Response to Patient Needs
- Lower Rejects and Scraps
- Fewer Product Recalls
- Increased Profit Margins

FbD Optimization Approach
Five-Step Methodology

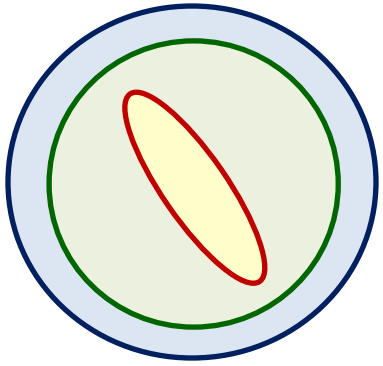


FbD
Scale-Up

10 Fold

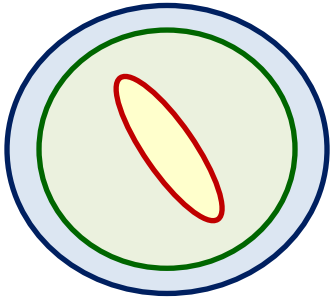
Generation

Confirmation



?

To be verified

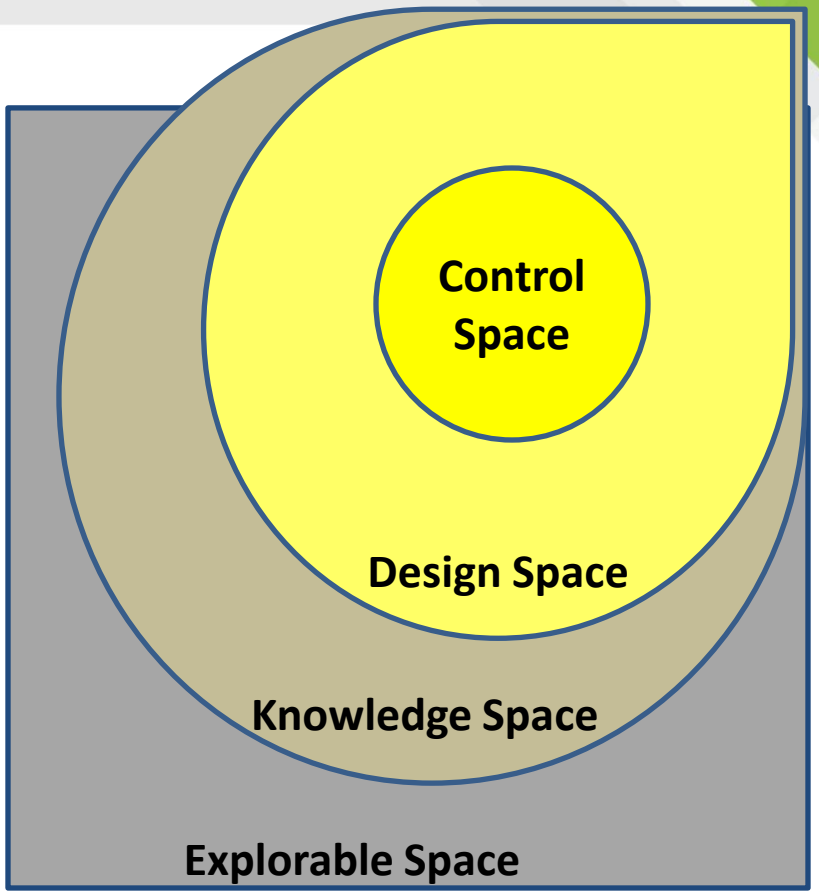


Lab/Pilot Scale Design Space

Commercial Scale Design Space

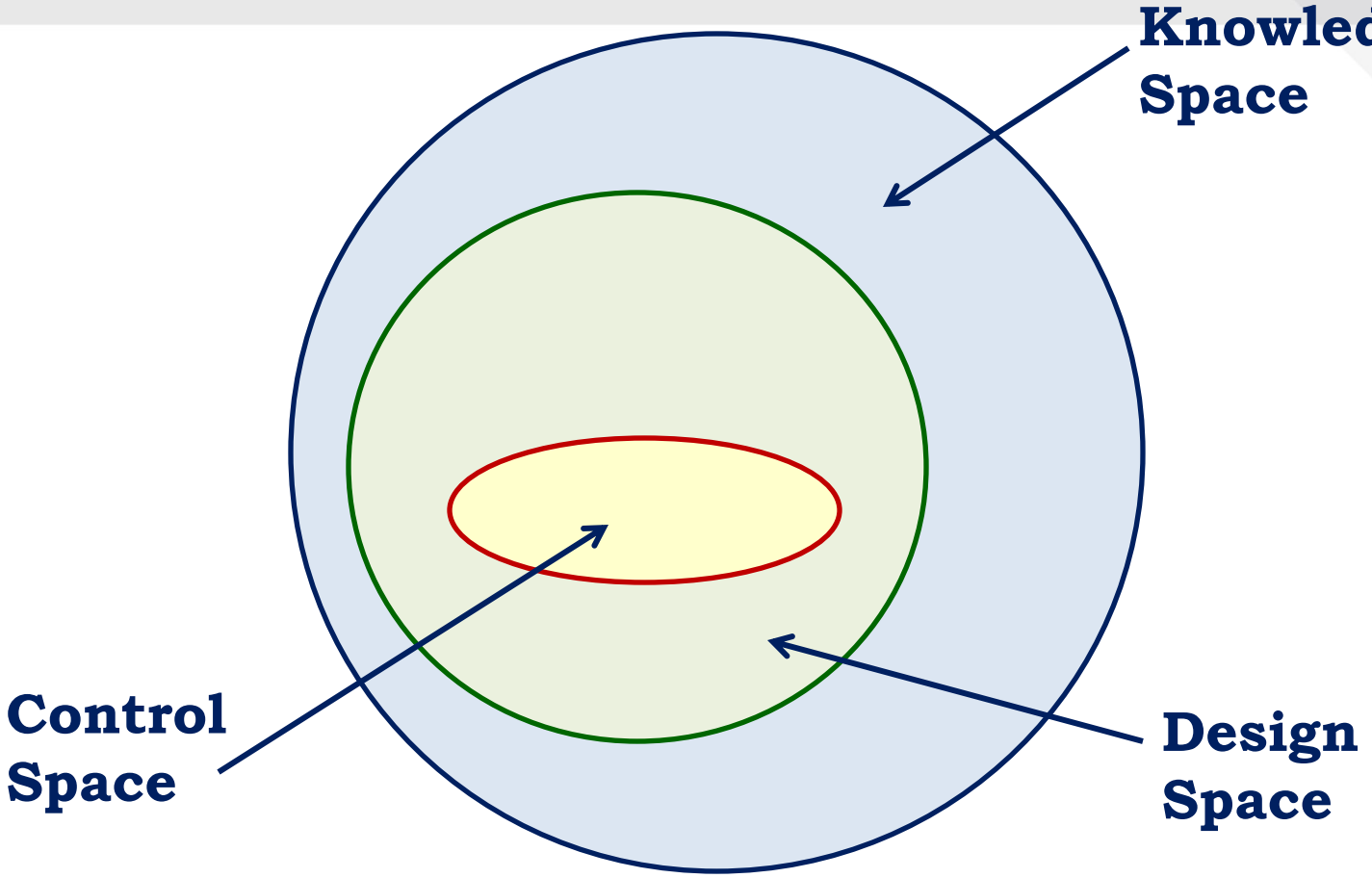
Design Space

- *It is a multidimensional combination and interaction of material attributes and/or process parameters which provides assurance of "Quality".*
- *Movement within the Design Space is not a "Change".*
- *Out of Design Space would require prior "Regulatory Approval".*

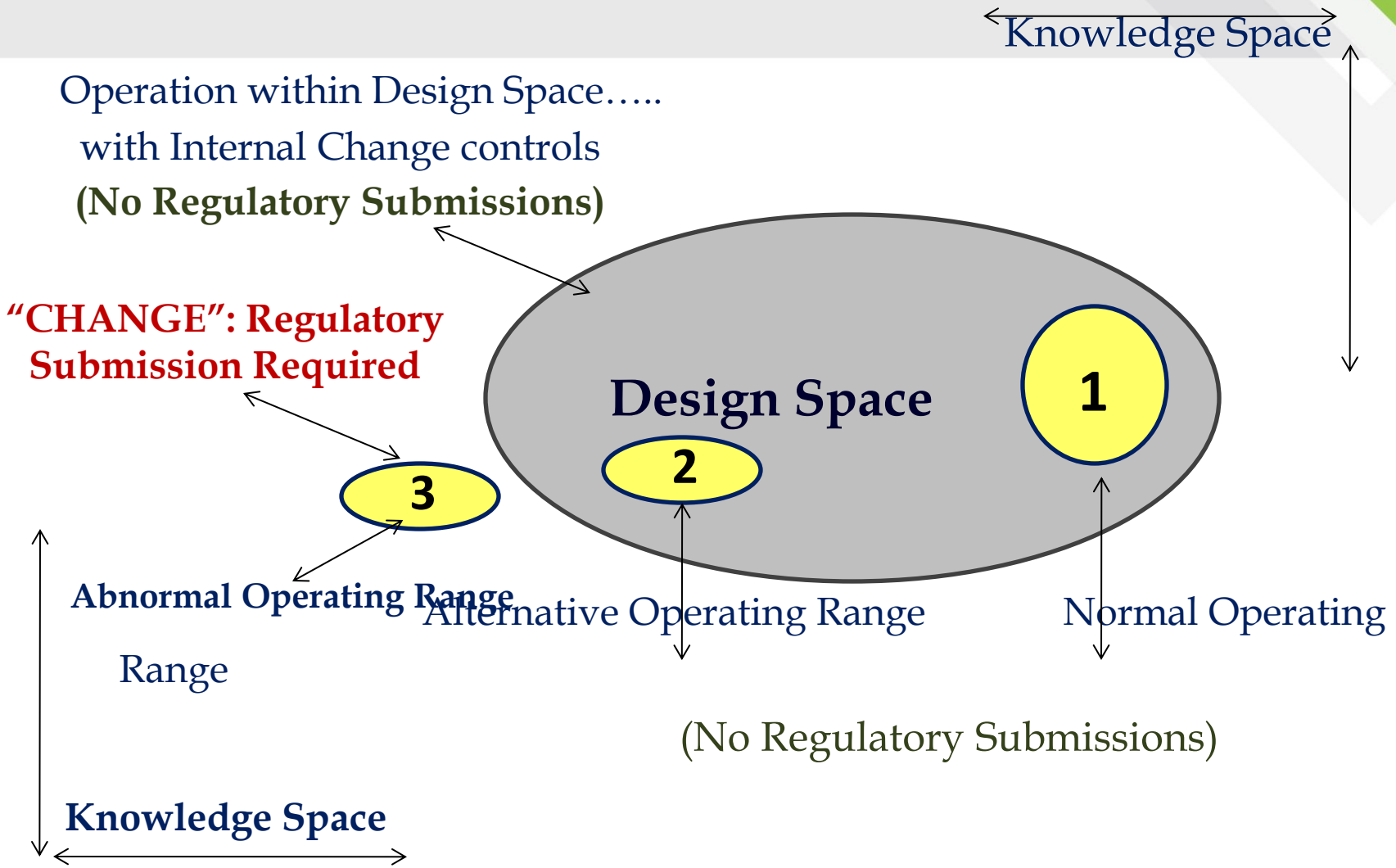


Design Space

It is Ideal to Move within the Control Space



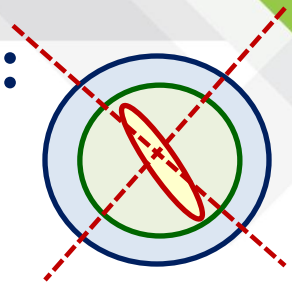
Design Space Variants



Design Space
"Regulatory" Importance

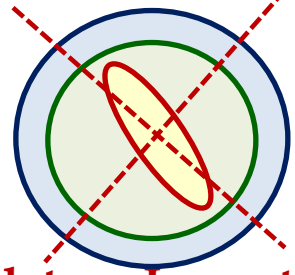
There can be Three types of Design Space:

- *Lab Scale Design Space* →



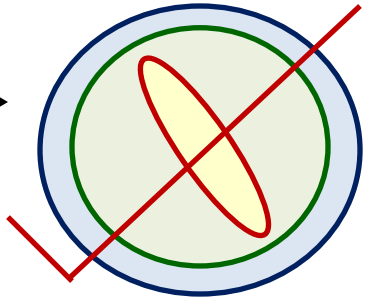
No Regulatory Importance

- *Pilot Scale Design Space* →



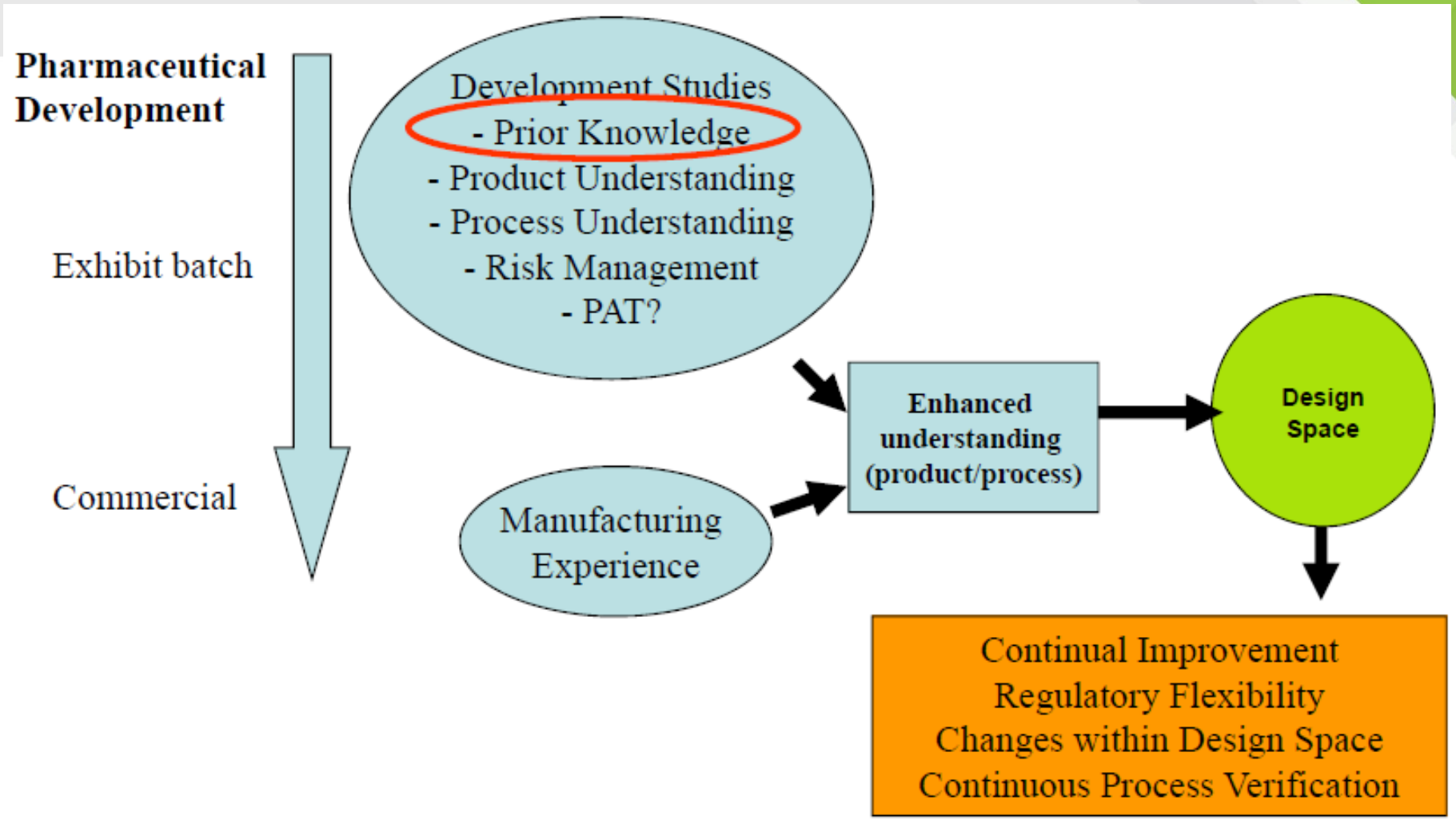
No Regulatory Importance

- *Commercial Scale Design Space* →



Meaningful Regulatory Importance

Hence…
We Have to Begin with End in the Mind

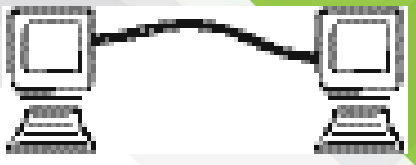


Systematic FbD Optimization implies…

SYNERGY

between

Drug Delivery, DoE and Computers



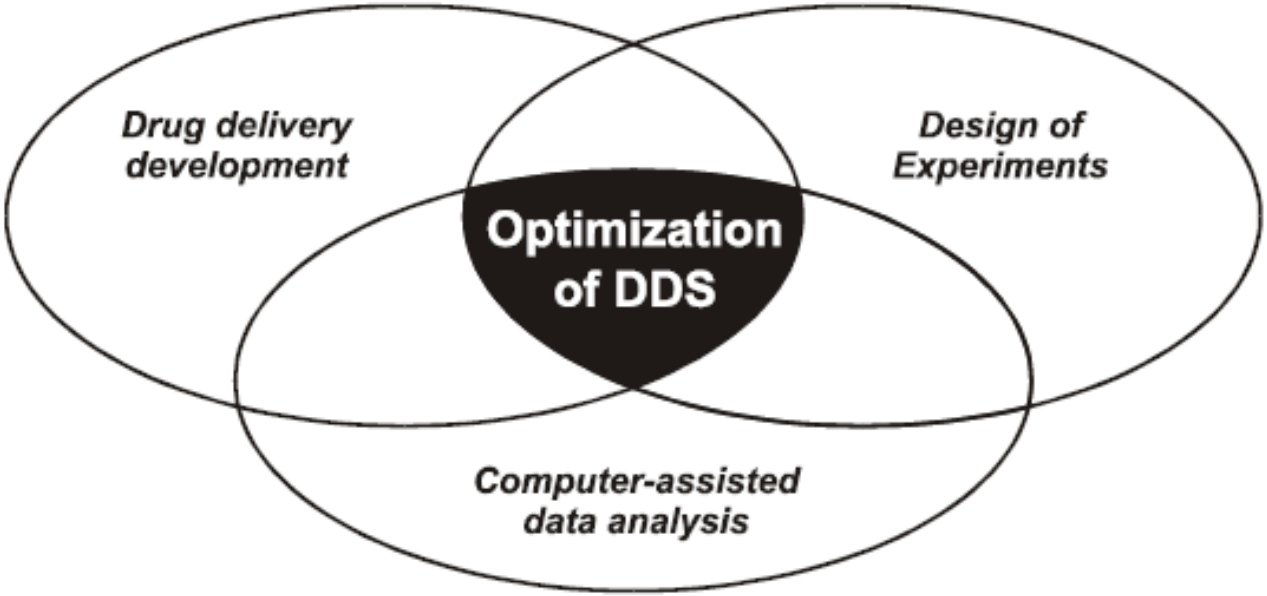


Figure adopted from Singh et al. *Crit. Rev. Ther. Drug Carrier Syst.* **22** (2005) 27-105

List of few Computer Software's for Systematic FbD Optimization

Multi Simplex G

FACTOP

SAS, SPSS, Systat

OPTIMA

JMP

Minitab

Design Expert & Analysis

Design Ease

NEMROD@

COED

CADD

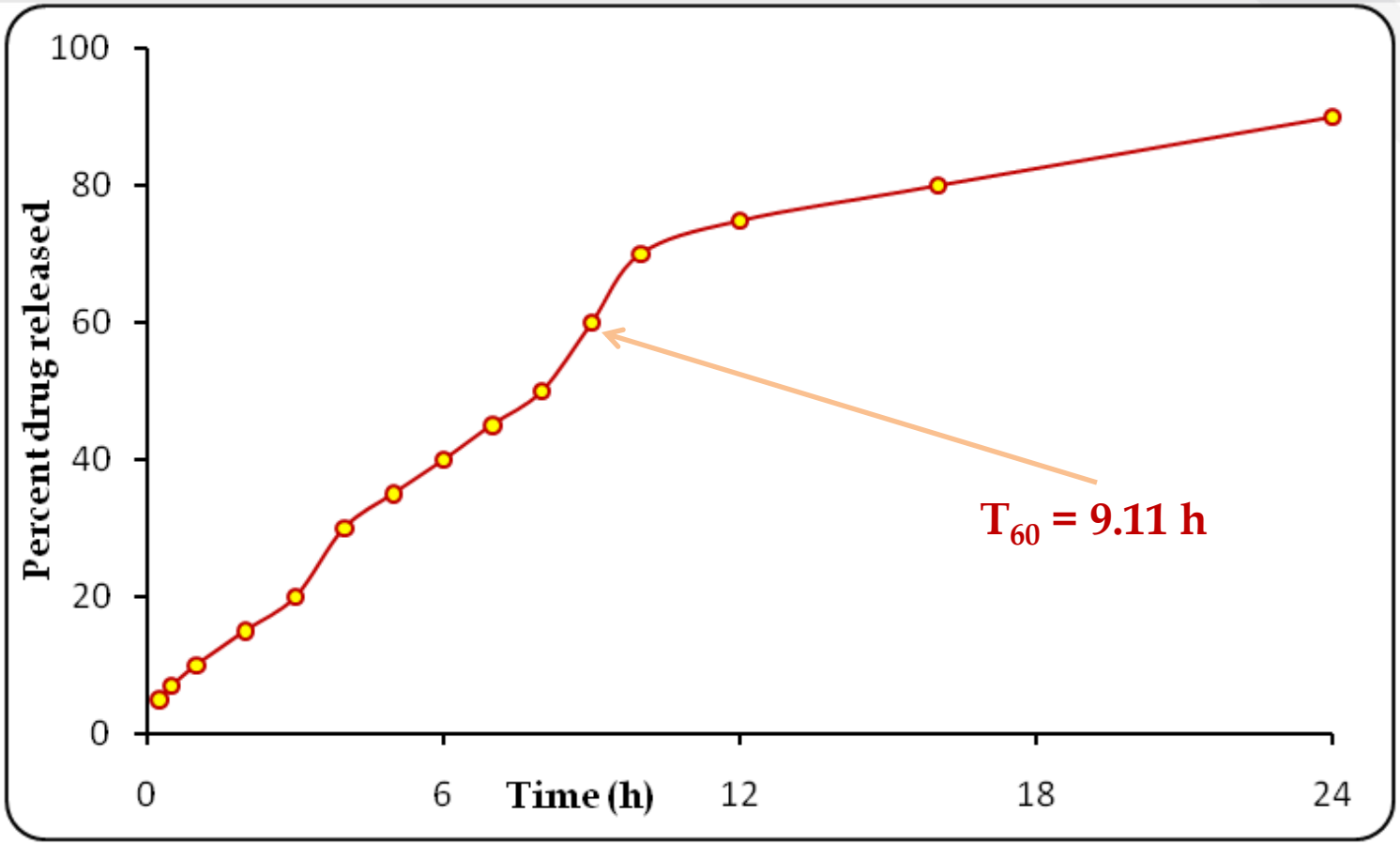
GRG2

ADDAD

FbD Optimization : Brute Force

Selection of the Desired Formulation

Case I



Desired Release Profile

FbD Optimization : Brute Force
Selection of the Desired Formulation

Case I

Feasibility Search for Optimized Formulation

	-1.00	-0.80	-0.60	-0.40	-0.20	0.00	0.20	0.40	0.60	0.80	1.00
-1.00	4.83	4.69	4.56	4.44	4.33	4.23	4.14	4.07	4.00	3.94	3.90
-0.80	5.07	4.93	4.81	4.70	4.61	4.52	4.45	4.40	4.35	4.32	4.30
-0.60	5.35	5.21	5.10	4.99	4.90	4.83	4.77	4.73	4.70	4.69	4.69
-0.40	5.67	5.53	5.41	5.31	5.22	5.15	5.10	5.06	5.04	5.04	5.06
-0.20	6.03	5.88	5.75	5.64	5.55	5.48	5.43	5.39	5.38	5.38	5.41
0.00	6.44	6.27	6.13	6.01	5.90	5.82	5.76	5.73	5.71	5.71	5.74
0.20	6.89	6.70	6.53	6.39	6.27	6.18	6.11	6.06	6.03	6.03	6.05
0.40	7.38	7.16	6.97	6.80	6.66	6.55	6.45	6.39	6.35	6.34	6.35
0.60	7.92	7.66	7.44	7.24	7.07	6.92	6.81	6.72	6.66	6.63	6.63
0.80	8.49	8.20	7.93	7.70	7.49	7.32	7.17	7.06	6.97	6.91	6.89
1.00	9.11	8.77	8.46	8.18	7.93	7.72	7.54	7.39	7.27	7.18	7.13

Selection of formulation having the desired parameter

FbD Optimization : Brute Force
Selection of the Desired Formulation

Case I

Feasibility Search for Optimized Formulation

	-1.00	-0.80	-0.60	-0.40	-0.20	0.00	0.20	0.40	0.60	0.80	1.00
-1.00	4.83	4.69	4.56	4.44	4.33	4.23	4.14	4.07	4.00	3.94	3.90
-0.80	5.07	4.93	4.81	4.70	4.61	4.52	4.45	4.40	4.35	4.32	4.30
-0.60	5.35	5.21	5.10	4.99	4.90	4.83	4.77	4.73	4.70	4.69	4.69
-0.40	5.67	5.53	5.41	5.31	5.22	5.15	5.10	5.06	5.04	5.04	5.06
-0.20	6.03	5.88	5.75	5.64	5.55	5.48	5.43	5.39	5.38	5.38	5.41
0.00	6.44	6.27	6.13	6.01	5.90	5.82	5.76	5.73	5.71	5.71	5.74
0.20	6.89	6.70	6.53	6.39	6.27	6.18	6.11	6.06	6.03	6.03	6.05
0.40	7.38	7.16	6.97	6.80	6.66	6.55	6.45	6.39	6.35	6.34	6.35
0.60	7.92	7.66	7.44	7.24	7.07	6.92	6.81	6.72	6.66	6.63	6.63
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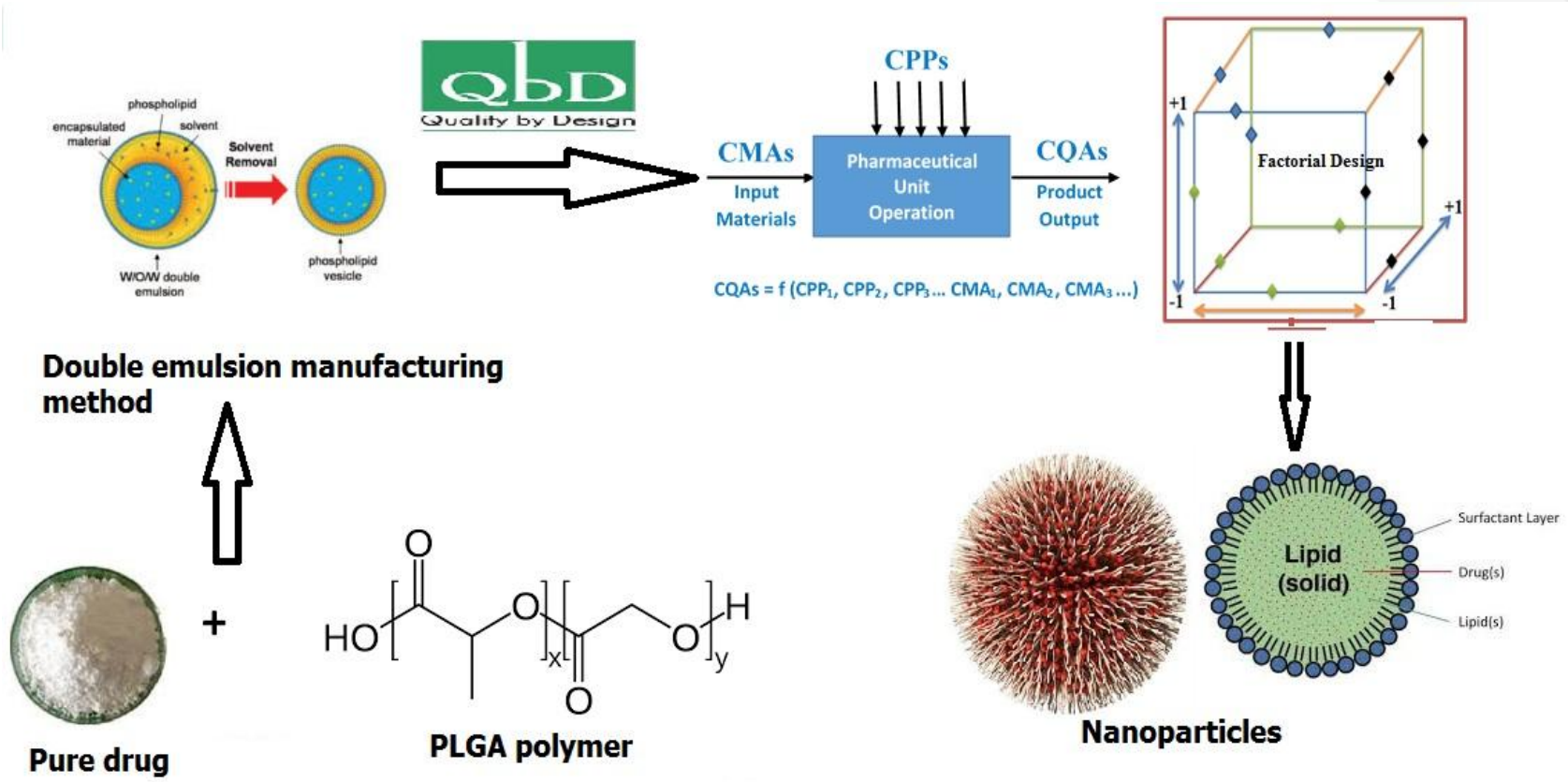
1.00	9.11	8.77	8.46	8.18	7.93	7.72	7.54	7.39	7.27	7.18	7.13

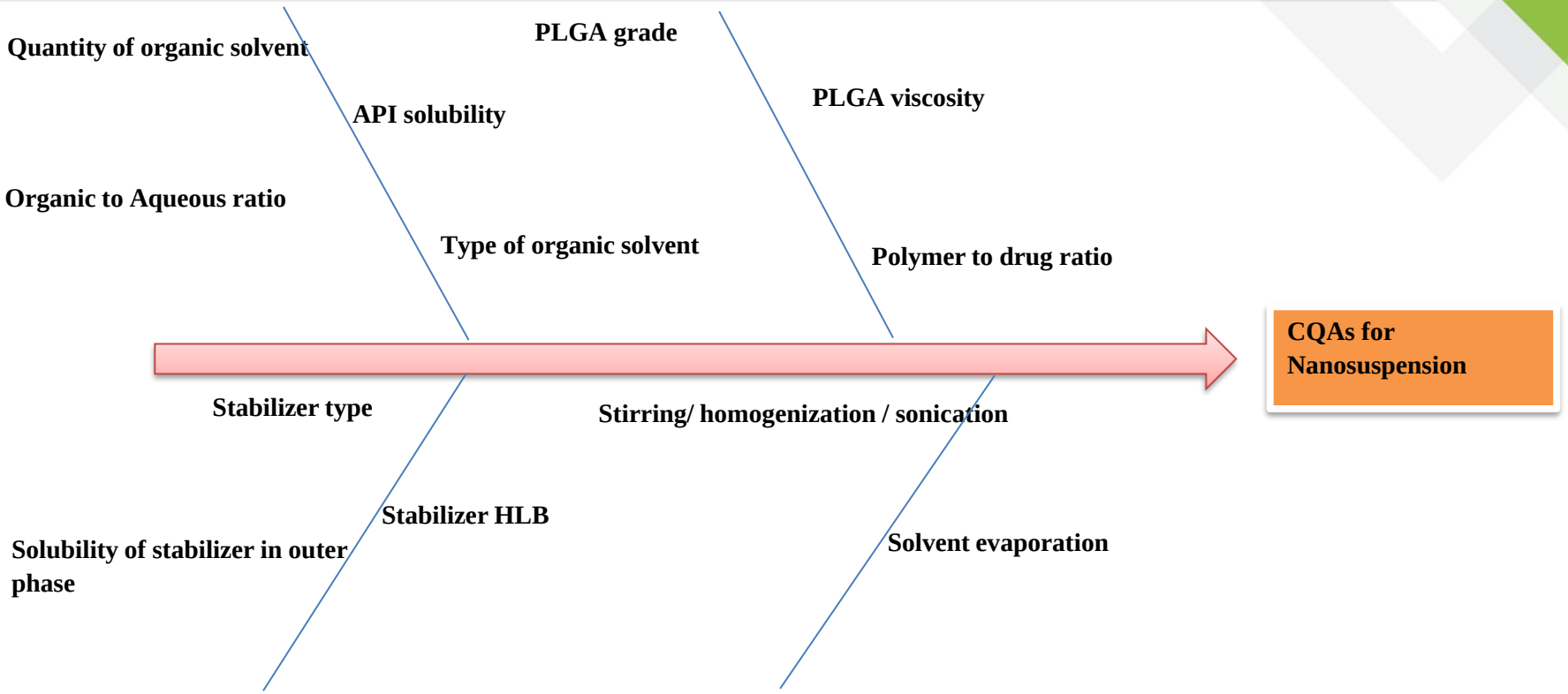
Formulation having levels of Polymer X and Y as -1.00 and 1.00 is the desired formulation


phospholipid
encapsulated material
solvent
Solvent Removal
W/O/W double emulsion
phospholipid vesicle
QbD
Quality by Design
CPPs
CMAs
Input Materials
Pharmaceutical Unit Operation
CQAs
Product Output
CQAs = f (CPP1, CPP2, CPP3 ... CMA1, CMA2, CMA3 ...)
Factorial Design
+1
-1
+1
-1
Double emulsion manufacturing method
Pure drug
+
HO
O
O
O
O
H
x
y
PLGA polymer
Surfactant Layer
Lipid (solid)
Drug(s)
Lipid(s)
Nanoparticles

Identification of CMAs, CFVs, CPPs for PLGA Nanoparticle produced by Double Emulsion (W/O/W).

Critical Material Attributes (CMA)	• API solubility in aqueous phase • Type of organic solvent • PLGA Grdae (Molecular weight of PLGA, LA/GA ratio, Viscosity of PLGA, Functional group of PLGA etc. • Type of Stabilizer • Solubility of stabilizer in outer aqueous phase • HLB value of Stabilizer • Viscosity of stabilizer
Critical Formulation Variables (CFV)	• Polymer/Drug ratio • Quantity of organic solvent • Ratio of organic solvent/ aqueous solvent • Concentration of W/O emulsifier (Primary Emulson) • [Text] • Concentration of Stabilizer
Critical Process Parameters (CPP)	• Stirring/Homogenization/ Sonication Time • Rate of addition of aqueous phase to organic phase • Solvent Evaporation Temperature

The fishbone diagram or Ishikawa diagram for QbD prospects of pharmaceuticals application of double emulsion method for PLGA loaded nanoparticles.



Conclusions

- The application of QbD tools in the development of pharmaceutical products is considered as “the best” approach to meet the product quality for the patients benefit. Hence, QbD is omnipresent in the entire product development lifecycle and can be considered as a versatile tool for attaining desired safety and efficacy of the drug products to meet the consumer demand.
- However, for complex formulation like PLGA nanoparticles, where many factors influence the quality of the product, the end product testing is not sufficient to define quality.
- QbD approach enables the manufacturer to understand and identify the variability induced by any factors during any unit operation of the product and subsequently helps to establish the controls to deliver consistent product quality.
- The ultimate goal of the QbD approach is to develop a pharmaceutical product with desired and consistent quality throughout its life cycle, fewer rejections, decreasing costs, and shortening review time for approval.

REFERENCES:

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- Singh B, Dahiya M, Saharan V, Ahuja N. (2005). Optimizing drug delivery systems using systematic "design of experiments." Part II: retrospect and prospects. Crit Rev Ther Drug Carrier Syst, 22:215–294.
- Computer-Aided Applications in Pharmaceutical Technology, Vol 13, James Swarbricks, James. G. Boylan, Marcel Dekker Inc, New York, 1996.

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- I extend my special to all the participants and delegates for hearing my session with patience.

ANY

QUERIES...

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Thank you all