Quality by Design (QbD)

More than Compliance – It is Survival

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Contents

- Paradigm Shift in dissolution requirements
- Some basics of QbD
- Knowledge Space
- CQA's of Product/Process/Method/Materials
- Risk Assessment
- DoE's – Theory, Examples & Control Strategy
- Food for Thought

Where do we come from?

- 1980: What happened when the product failed in dissolution testing? It was dissolved forcefully.
- 2015: Now not only that product failure is a concern but variation at even one time point is a cause of concern?
- What has been the cause of this transformation?
- Can 6 or 12 tablets predict the dissolution of batch having 5 Lac tablets?

Driving Force Behind PAT & QbD

“Quality can not be tested into products; it has to be built in by design”(ICH Q8/ Q11 on product/ drug substance development)

What is Quality By Design ?

As per ICH Q8/Q11 :

"QbD is a systemic approach to development that begins with predefined objectives & emphasizes product & process understanding and process control, based on sound science & quality risk management."

Important References for QbD & PAT

ICH Q8(R2): Pharmaceutical Development

ICH Q9 : Quality Risk Management

ICH Q10 : Pharmaceutical Quality System

ICH Q11 : Development & Manufacture of DS

QbD, Buzz Word ? More chewed than swallowed ?

BLAH,
BLAH,
BLAH…

QbR of QbD

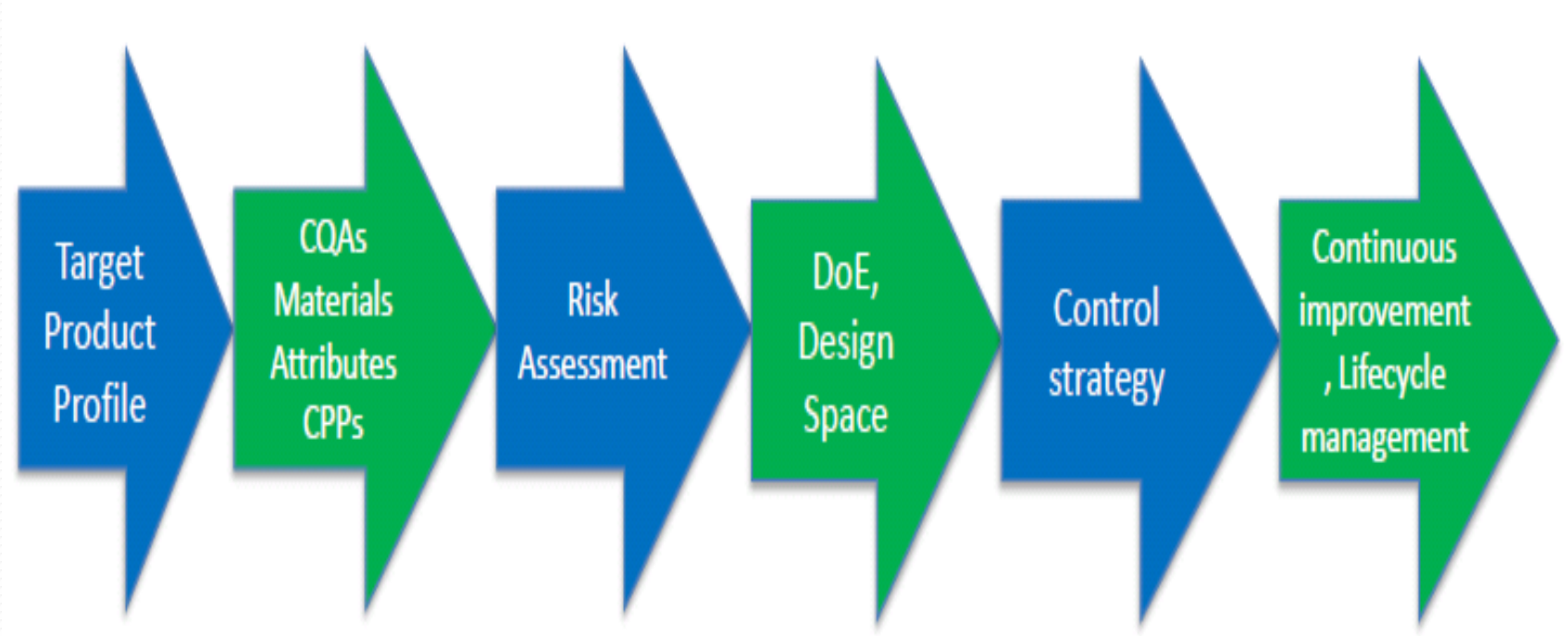
QbR : Question based Review :

- Is it difficult to follow? How to begin?
- Is it a very costly exercise?
- Is it mandatory?
- Can it be followed by small companies?
- To what extend PAT’s are required?
- Is it only for Product Development?

Do you Have?

- On line Conductivity meters
- On line pH meters
- On line TOC Meters
- Temp record charts
- Continuous monitoring of temp/RH/Differential pressures
- Continuous Particle monitoring

QbD Approach (Important Stages)

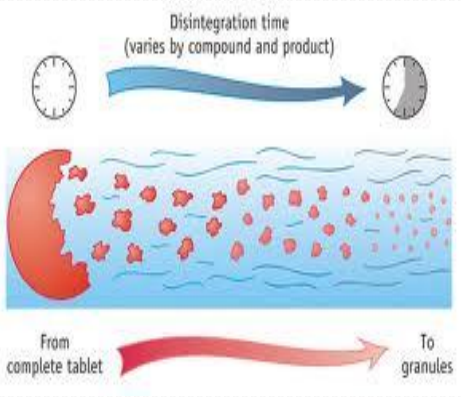


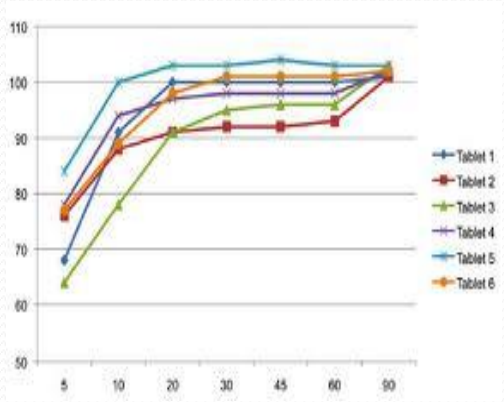
Defining 4 D's

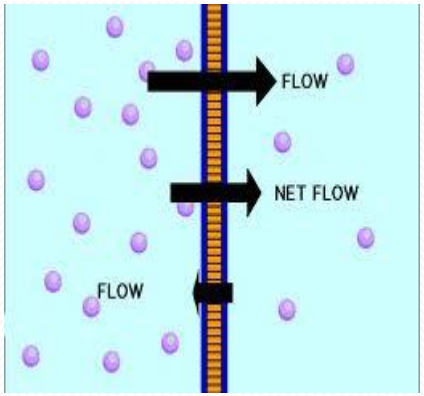
- Disintegration time is the time required for a dosage form to break up in to granules of specified size
- Dispersion is actually meant to distribute the mass evenly thus moving the mass from higher concentration to lower concentration
- Dissolution is the rate of mass transfer from a solid surface into the dissolution medium or solvent under standardized conditions
- Diffusion refers to the process by which molecules intermingle as a result of their kinetic energy of random motion.

Understanding Dissolution Science

- Disintegration
- Dispersion
- Dissolution
- Diffusion







Sink Conditions

- Sink condition refers to the volume of medium which is at least three times that is required in order to form a saturated solution of API
- In the absence of sink conditions, investigate methods to enhance solubility, e.g. use of a surfactant
- If a surfactant is used, its concentration should be properly justified (e.g. <2% SLS).

Quality Target Product Profile

QTPP Element	Target	Justification
Dosage Form	Tablet	To match innovator
Dosage design	Immediate Release	To match innovator
Route of Admin.	Oral	To match innovator
Pharmacokinetics	Matching Cmax/Tmax	To pass BE studies
Container/Closure	Must provide adequate protection & Cost Efficient	For stability of product & financial viability of the firm
Stability	Stable for 36 Months	To match innovator
Score Line	To have a deep score	Tablet should break in 2 equal halves

QA's of API (Related to Dissolution)

Quality Attributes	Target	Is this CQA ?	Justification
Appearance	Color & Shape	No	Not linked to Safety & Efficacy
Assay & Particle Size	100% w/w & matching spread	Yes	Impacts dissolution
Moisture Content	< 0.5%	Yes Exceptions ?	Higher moisture leads to polymorphic change in some cases
Intrinsic Dissolution	NLT 80%(Q) in 20 Mts	Yes	Impacts Bioavailability of Drug Product
Individual unknown Impurities	NMT 0.1%	No	Does not impact dissolution of the API/Drug Product

QA's of DP (Related to Dissolution)

Quality Attributes	Target	Is this CQA ?	Justification
Score line	To have similar dissolution for 2 halves	Yes	Patient should get same drug content
Hardness	To have optimum hardness	Yes	To facilitate disintegration & dissolution of product
Content Uniformity	To have similar drug content in all units	Yes	Impacts dissolution

Establishing Better Linkage

DP CQAs	Drug Substance Attributes		
	Particle Size	Polymorphic Nature	Moisture Content
Assay	Medium	Low	High
CU	High	Low	Low
Dissolution	High	Medium	Low
Impurities	Low	Low	High

Risk Factors of Dissolution Testing

- Proper Deaeration of media
- Calibration of Apparatus
- Selection of filters
- Finding out Discriminatory media
- HPLC or UV method
- Collection of samples
- Result reporting
- Investigation of stability failures
- Method validation/ method verification
- In Vivo/ In Vitro correlation
- Let us learn from case studies!

Importance of Deaearation

	Aceclofenac Tablets 100mg		
	With degassing	Without degassing	
Jar -1	98	99	
Jar -2	97	86	
Jar -3	102	94	
Jar -4	94	104	
Jar -5	98	92	
Jar -6	99	98	
RSD			
Mean	**98**	**96**	

- RSD 2.7 % 6.5 %

Importance of proper calibration

Buprenorphine tablets 8mg							
Jar -1	89						
Jar -2	86						
Jar -3	**100**	(Paddle wobbling)					
Jar -4	91						
Jar -5	88						
Jar -6	87						

Importance of proper filter

Name	Losartan Potassium and Amlodipine tablets					
Dissolution Medium	Buffer pH 4.5					
Component	**Losartan Potassium**			**Amlodipine**		
Type of filters used	**NYLON**	**PTFE**	**PVDF**	**NYLON**	**PTFE**	**PVDF**
	% Release			% Release		
Tab 1	6	99	99	68	98	98
Tab 2	16	103	102	69	101	97
Tab 3	26	99	99	71	102	101
Tab 4	33	98	100	77	99	102
Tab 5	43	100	100	79	101	102
Tab 6	47	102	102	81	99	101
Mean	29	100	100	74	100	100
SD	15.76	1.94	1.37	5.53	1.55	2.14
% RSD	**54.34**	1.94	1.37	**7.47**	1.55	2.14
Min	6	98	99	68	98	97
Max	47	103	102	81	102	102
Remarks	PVDF – Polyvinylidene fluoride membrane filter PTFE - Polytetrafluoroethylene membrane filter					

Deaeration Method

USP/BP: Heat the medium while stirring gently to filter having a porosity of 0.45 micron or less, with vigorous stirring, and continue stirring under vacuum for about 5 minutes. Other validated techniques for deaeration can be used .

IP too mentions the requirement of deaeration.

How many of you have validated your Deaeration Technique?

Risk Assessment of Method (Scale of 1-5)

Risk	Probability	Severity	Detection	RPN
Improper IVIVC Correlation	3	5	4	60
Non discriminative method	3	4	3	36
Improper Deae-ration	3	3	3	27
Improper Filter	3	2	2	18

Prerequisite of successful DoE

- Basic statistical knowledge
- Specialized training on software
- Mimic the real life scenario
- Use similar equipments, Instruments in terms of MOC & principle of operation
- Similar measurement tools

Conventional v/s DoE approach

CONVENTIONAL APPROACH

- Changing one factor at a time.
- May not give real optimum output
- Leads to many experiments and little information.
- Variability may not addressed
- No quantification of interactions.

DOE APPROACH

- Changing all factors same time.
- Investigates entire region in a organized way & provide reliable basis for decision making.
- Provides more precise info. with fewer experiments.
- Variability is addressed
- Quantification of interactions.

Design of experiments (DoE)

Definition:

"*A structured, organized method for determining the relationship between factors affecting a process and the output of that process.*"

Applications :

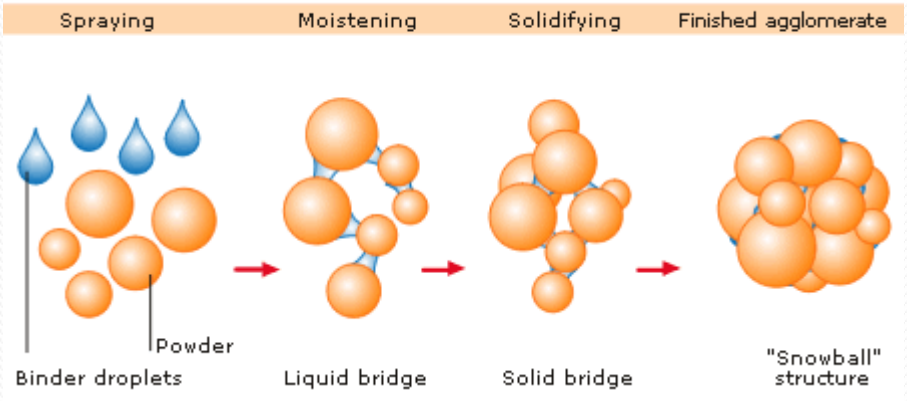
- Development of new products/processes/ analytical methods.
- Enhancement of existing products & processes.
- Screening important factors.
- Minimization of production costs & pollution
- Development of Analytical Methods

Steps involved in DOE

- Define Factors (material, process, equip./environment)
- Define Responses (critical quality attributes)
- Create Design
- Construct Model
- Evaluate Model
- Interpret & Use Model (Make Decisions)

Process Attributes

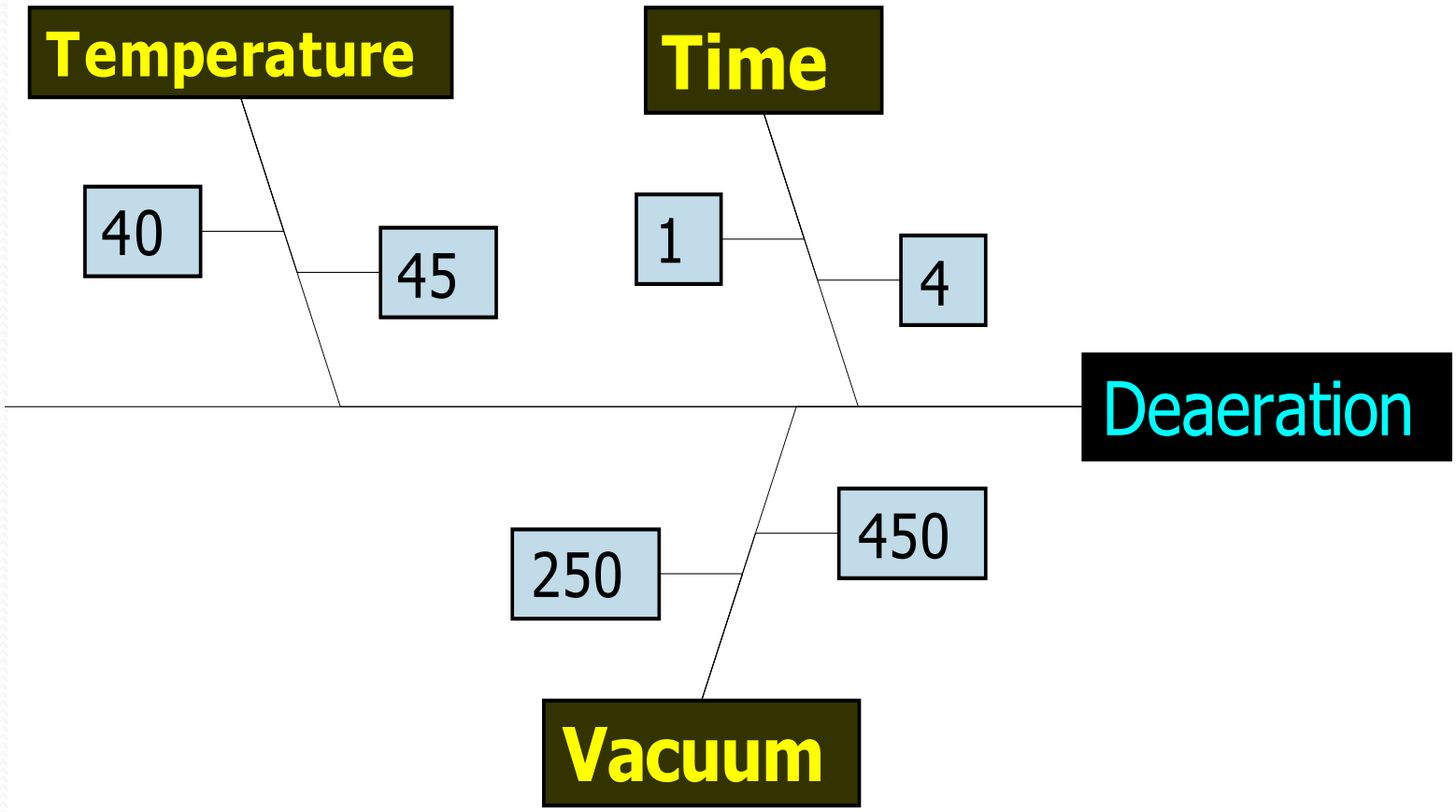
- Qualitative and quantitative excipient changes
- Manufacturing parameters
  - Granulation
  - Lubrication
  - Blend time
  - Compression force
  - Drying parameters



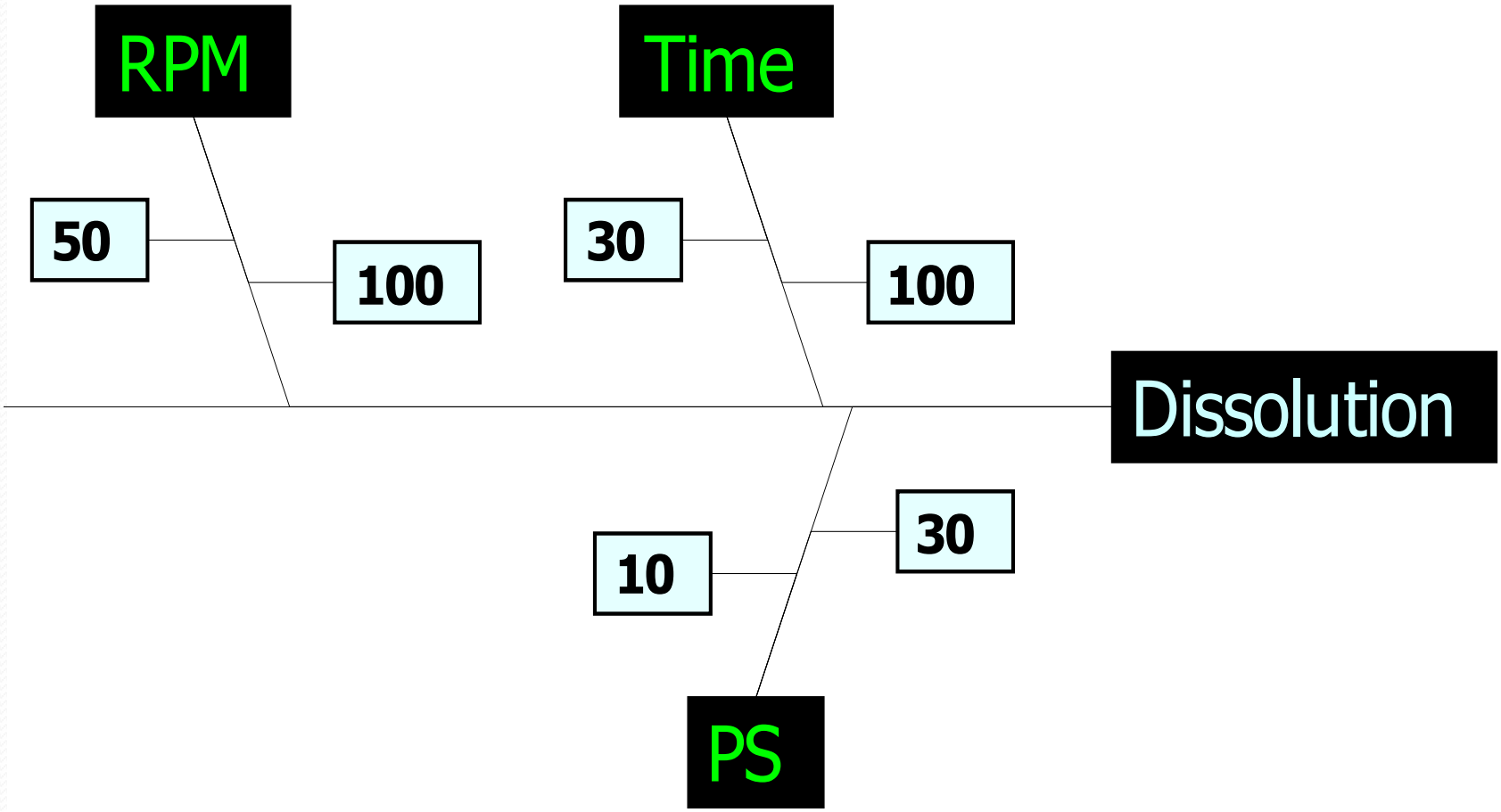
SOME DoE EXAMPLES

(CREATED ON PAPER JUST FOR ILLUSTRATION)

Optimization of Deaeration Procedure



Dissolution Design of Experiments



Control Strategy

- Do extensive literature search
- Do not rely solely on Pharmacopeial/OGD methods
- Minimize the number of invalidated OOS's
- Do not over commit on the specifications
- Last but not the least, implement QbD
- But remember that it is not a magic stick

Food for thought …

Within specification Investigation?

- Am I crazy?
- But tell me as much as product can fail in analysis by mistake, can it not pass also by mistake ? Think over!
- I feel it will be a future requirement?

Mass Balance application to Dissolution

Food for thought …

OOS Result obtained during BE limit?

Current Scenario?

- Most probably CRO has done a mistake?
- Analysis has been done wrongly?
- BE protocol was not proper?
- There was lack of control on volunteers?
- I am right, you are wrong?

Why not apply OOS to BE failures?

Food for thought

Rationality of BE Studies?

- Many people prefer to use the same batch of innovator for product development, analysis of exhibit batch, stability, pilot BE studies, pivotal BE studies etc. Why?
- People have observed difference in innovator product from batch to batch? Why?
- What is the consistency that we are talking about?

Is that the genesis of QbD?

References

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- USP 35 <711> Dissolution and <724> Drug Release <1088> In-Vitro and In-Vivo Evaluation of Dosage Forms
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THANK YOU

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