Design Space – A Risk Based Approach

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Definition of Design Space

Design Space is:

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

  ICH Q8(R2) (Step 4, August 2009), "Pharmaceutical Development", page 7.

- We interpret Quality to mean patient safety and efficacy.
- We do not interpret assurance to mean 100% certainty.

Example: Oral Solid Dosage Granulation and Compression

Granulation

- Three HSWG parameters (Xs)
  - Quantity of water added
  - Rate of water addition
  - Wet massing time

Compression

- Three Compression parameters (Xs)
  - Main compression force
  - Main compression/pre-compression ratio
  - Speed

Critical Quality Attributes

Three CQAs (Ys)
- Disintegration time: < 15 minutes (A's)
- Friability: < 0.8 % loss after 12 min at 25 rpm
- Hardness: 8-14kp

Design Space Definition

Design space consists of the set of all values and combinations of the controllable parameters (X's) that are predicted to yield all of the critical quality attributes (Y's) within their specifications (A's) with a probability of at least 1-α.

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

Experience with existing processes may provide input to the establishment of a practical target value for α.

This definition does not provide a sharp "edge of failure". Values outside the design space are not doomed to fail and values inside are not guaranteed to succeed.

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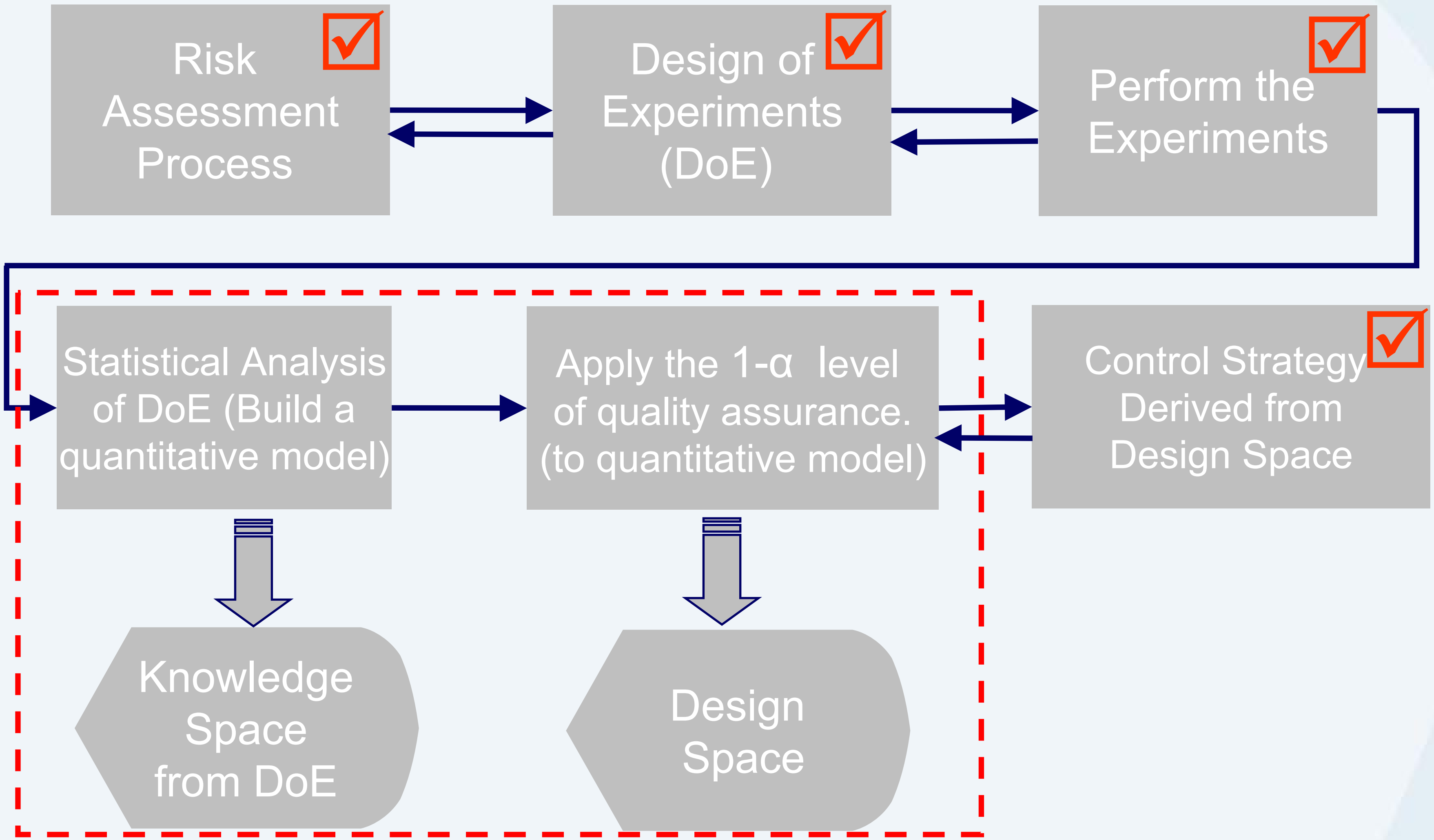

Example: Oral Solid Dosage Granulation and Compression

Granulation

- Three Granulation parameters (Xs)
  - Quantity of water added
  - Rate of water addition
  - Wet massing time
- 7 combinations plus two centre points on granulation

Compression

- Three Compression parameters (Xs)
  - Main compression force
  - Main compression/pre-compression ratio
  - Speed
- 8 combinations plus three centre points on compression

CQAs

Three CQAs (Ys)
- Disintegration time: < 15 minutes (A's)
- Friability: < 0.8 % loss after 12 min at 25 rpm
- Hardness: 8-14kp

All granulation combinations combined with all compression combinations to give a total of 99 runs

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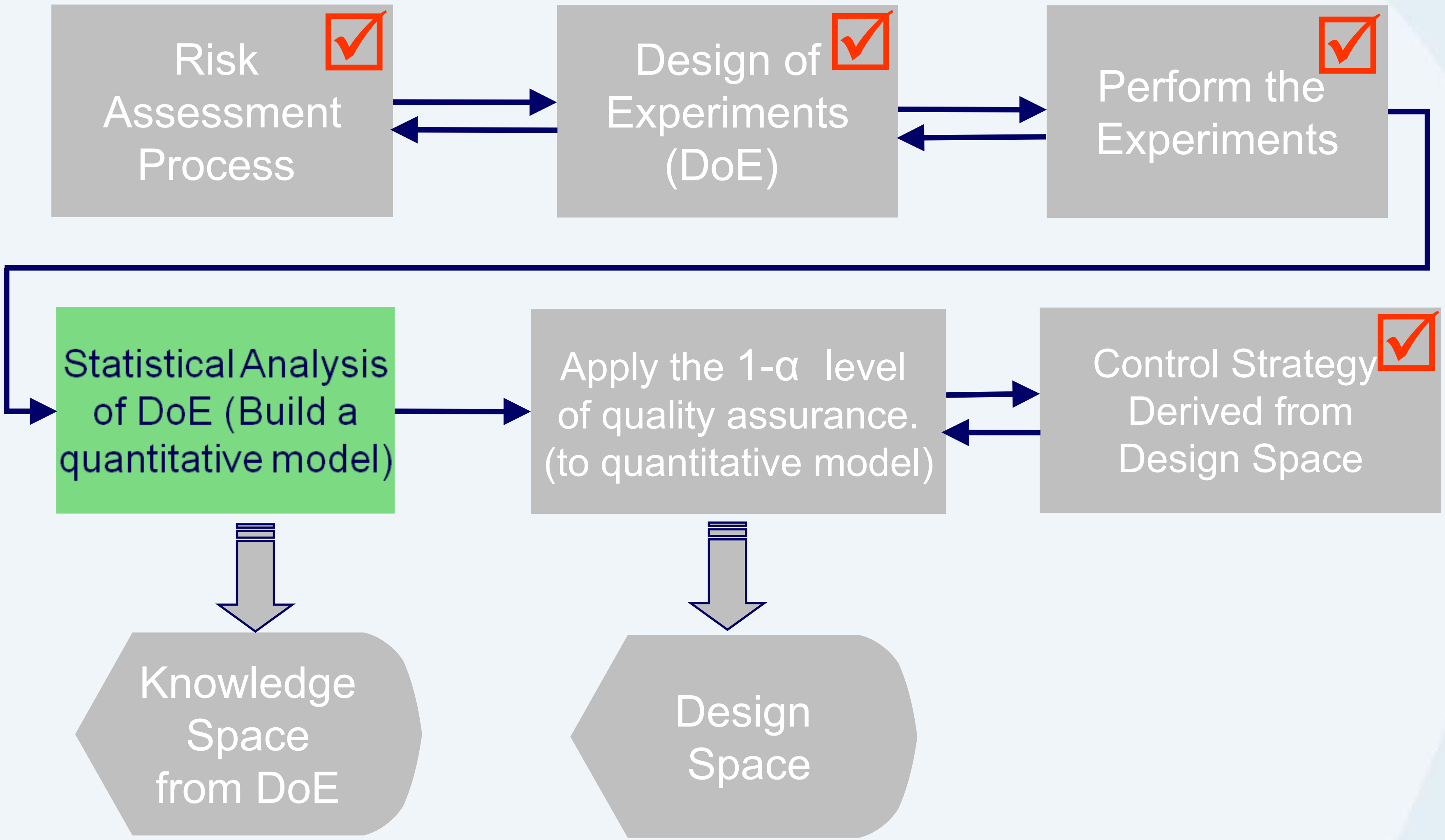

Example: OSD Granulation and Compression Analysis – Seemingly Unrelated Regression Models

Disintegration Time

1. Water Addition Quantity
2. Water Addition Rate
3. Wet Massing Time
4. Main Compression Force
5.

Interactions: 2 by 4; 3 by 4

Friability

1. Water Addition Quantity
2.
3. Wet Massing Time
4. Main Compression Force
5. Ratio: Main to Pre Compression Force

Interactions: 1 by 5; 3 by 4; 3 by 5; 1 by 3 by 4

Hardness

1. Water Addition Quantity
2. Water Addition Rate
3. Wet Massing Time
4.
5.

Interactions: 1 by 2; 2 by 3; 1 by 3

Correlation Matrix			
CQA	Dis Time	Friability	Hardness
Dis Time	1.0000		
Friability	0.3362	1.0000	
Hardness	0.1387	0.01602	1.0000

Table of Probabilities of Passing Specs for given x

Granulation Factors			Compression Factors		Probability of Meeting Specifications			
Water Addition Quantity	Water Addition Rate	Wet Massing Time	Main Compression Force	Main to Pre Compression Force	Joint Probability	Disintegration Time	Friability	Hardness
31.0	27.4	4	15	0	0.8255	0.9917	0.9835	0.8465
31.6	26.6	4	15	0	0.8243	0.9929	0.9709	0.8553
31.0	29.0	4	15	0	0.8231	0.9954	0.9856	0.8391
31.0	29.0	4	15	0.3	0.8231	0.9945	0.9825	0.8416
31.0	28.6	4	15	0	0.8230	0.9941	0.9830	0.8422
31.0	28.6	4	15	0.3	0.8229	0.9953	0.9807	0.8430
31.0	27.8	4	15	0	0.8228	0.9909	0.9809	0.8454
31.6	27.0	4	15	0	0.8215	0.9936	0.9699	0.8524
31.0	28.2	4	15	0.3	0.8210	0.9951	0.9791	0.8421
31.0	26.6	4	15	0	0.8201	0.9888	0.9787	0.8477
31.6	27.8	4	15	0	0.8197	0.9951	0.9763	0.8442
30.5	28.6	4	15	0	0.8191	0.9929	0.9886	0.8344
31.0	26.2	4	15	0	0.8188	0.9886	0.9761	0.8477
31.0	27.8	4	15	0.3	0.8188	0.9940	0.9767	0.8443

Control Parameter Combinations

Marginal Probabilities

[1] This is only a small portion of a much bigger table.

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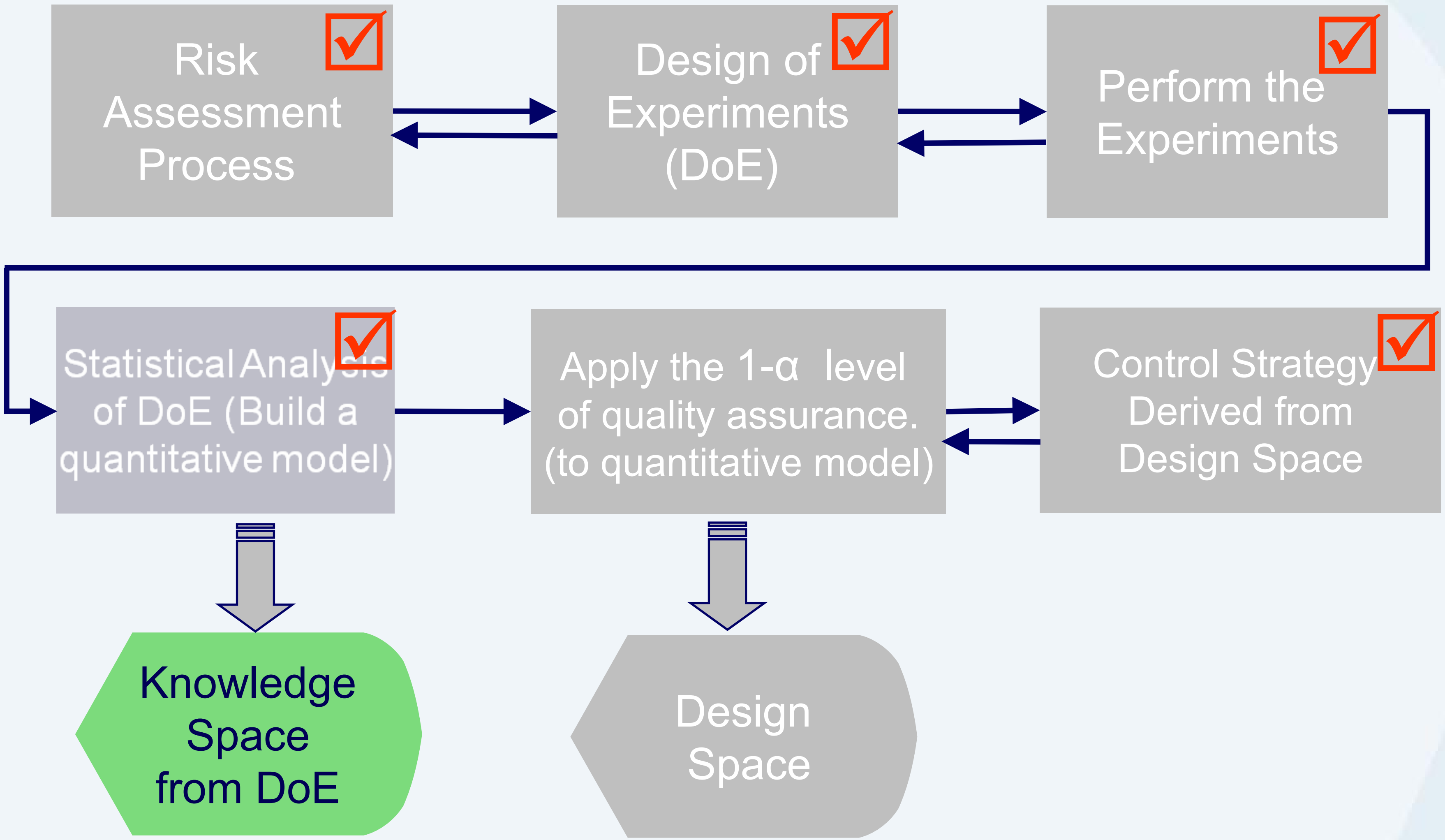
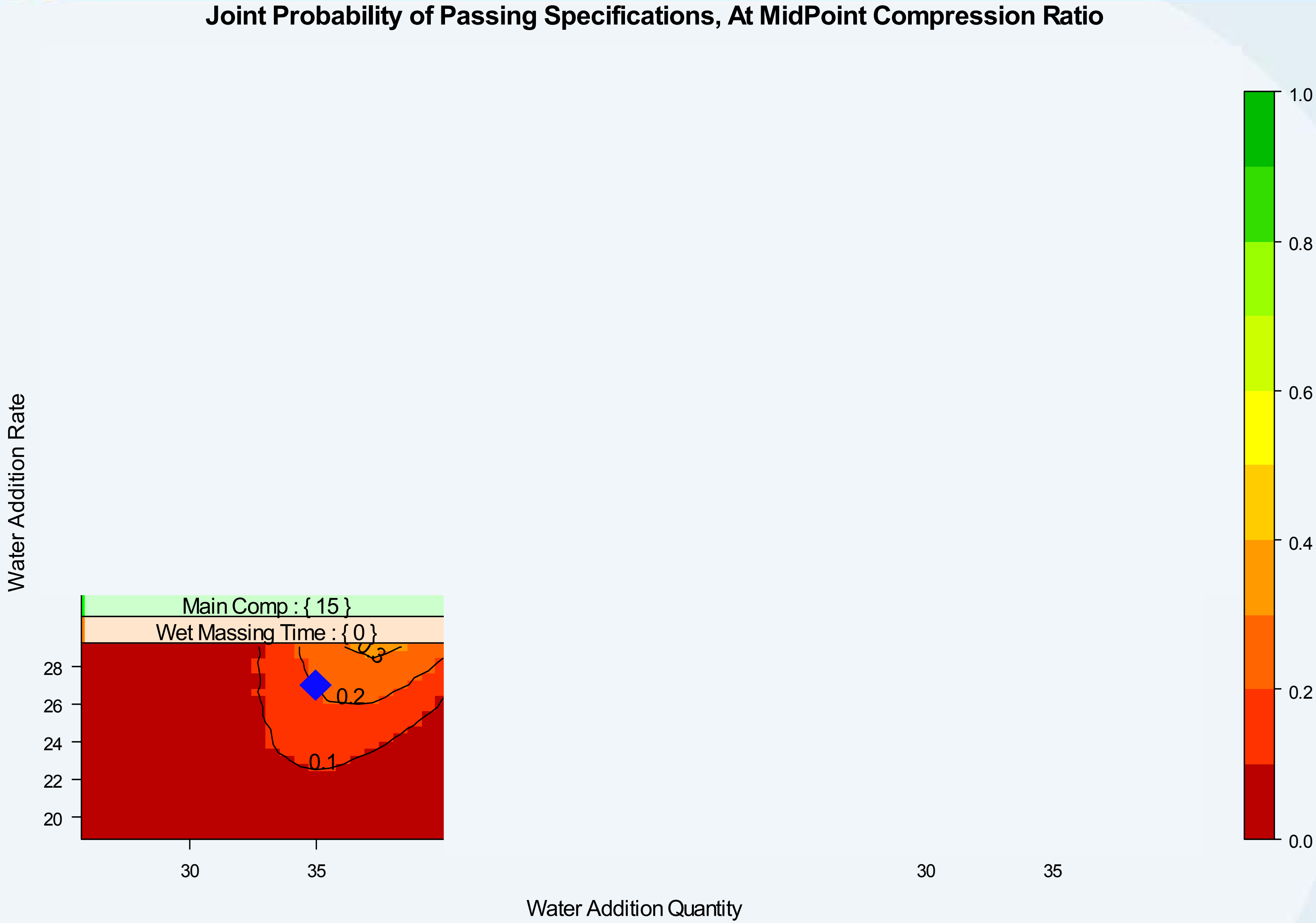


Example: Displaying the Knowledge Space



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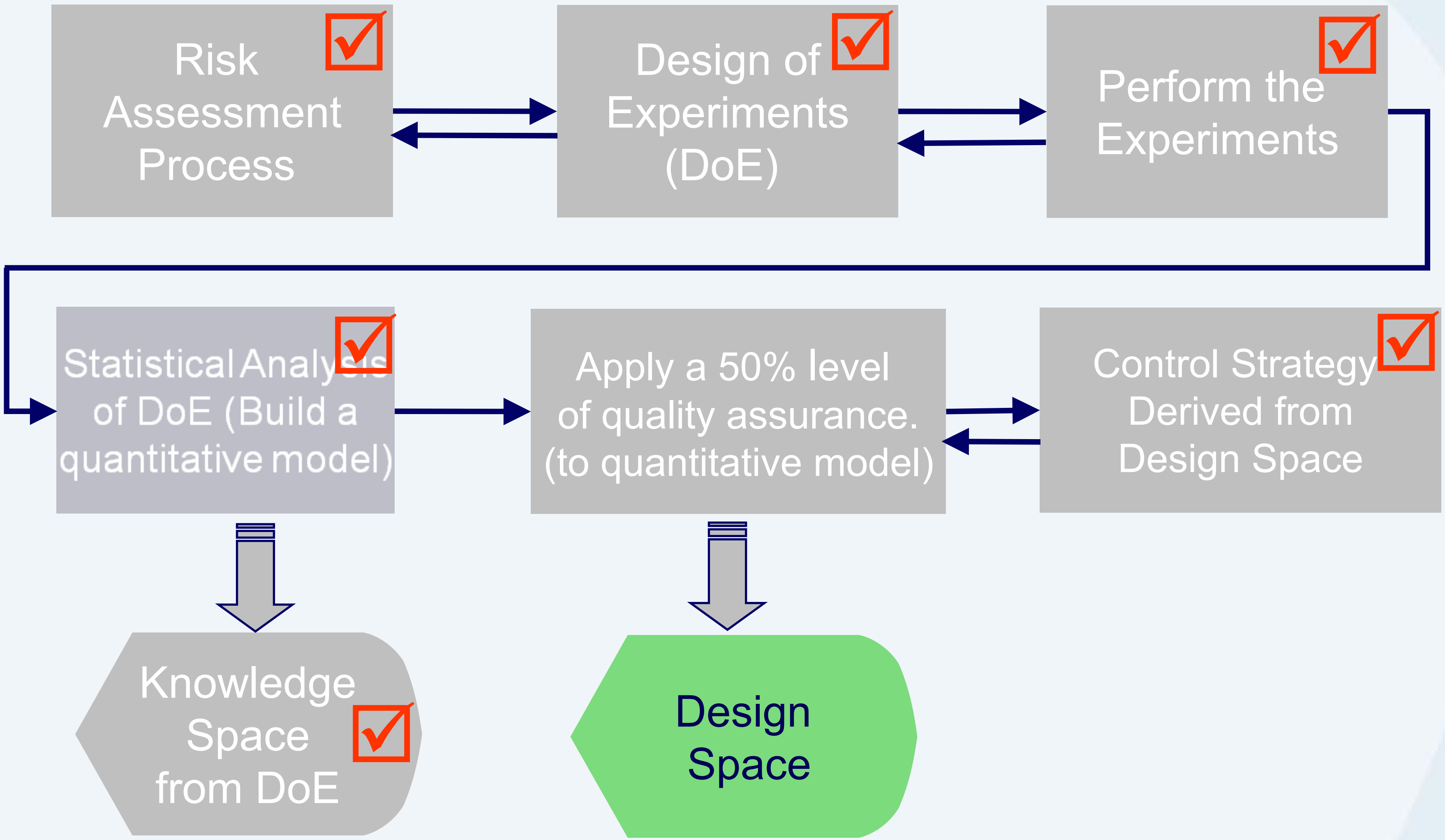
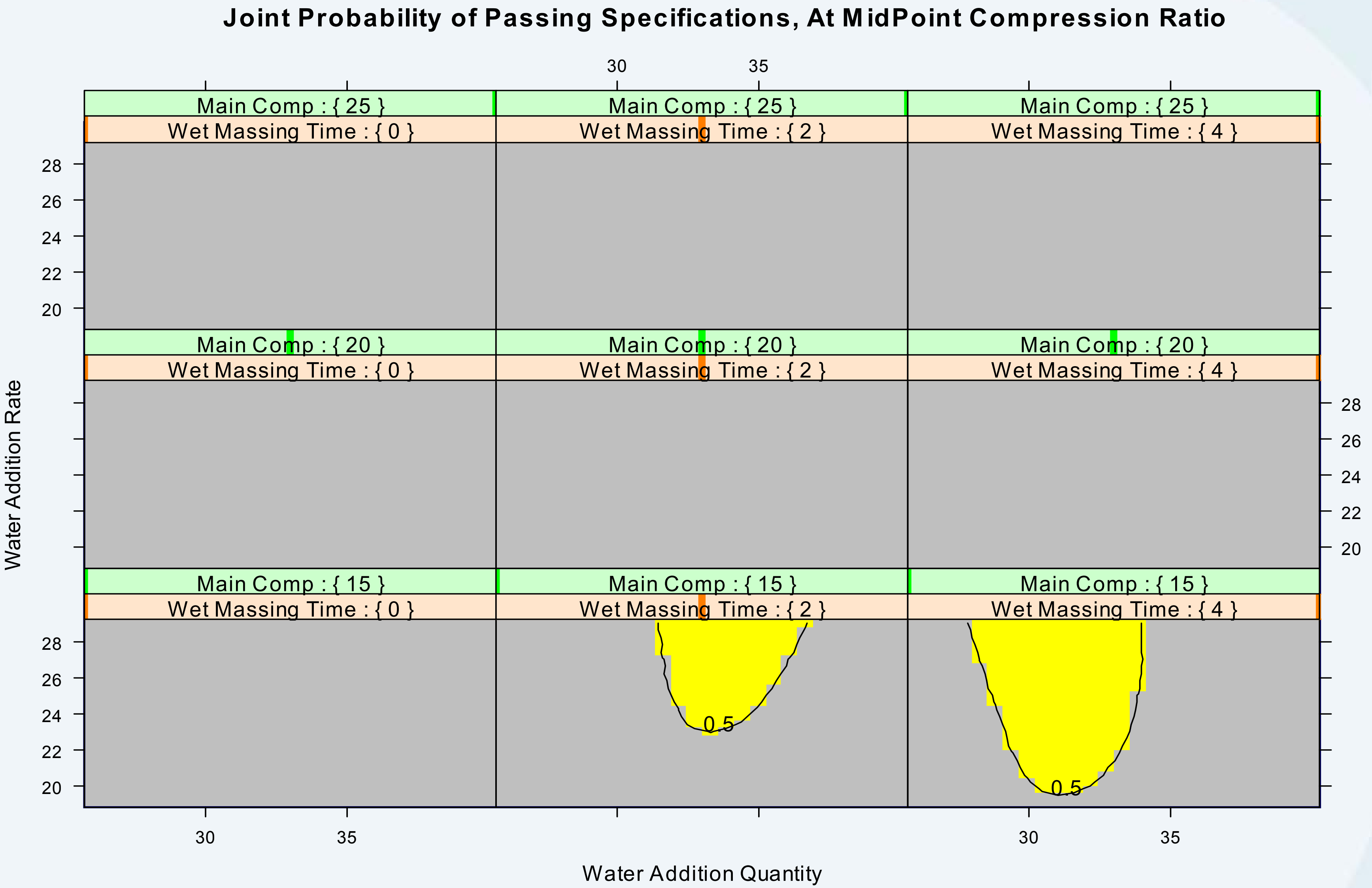


Example: OSD Granulation and Compression Design Space, with 1-α = 50%



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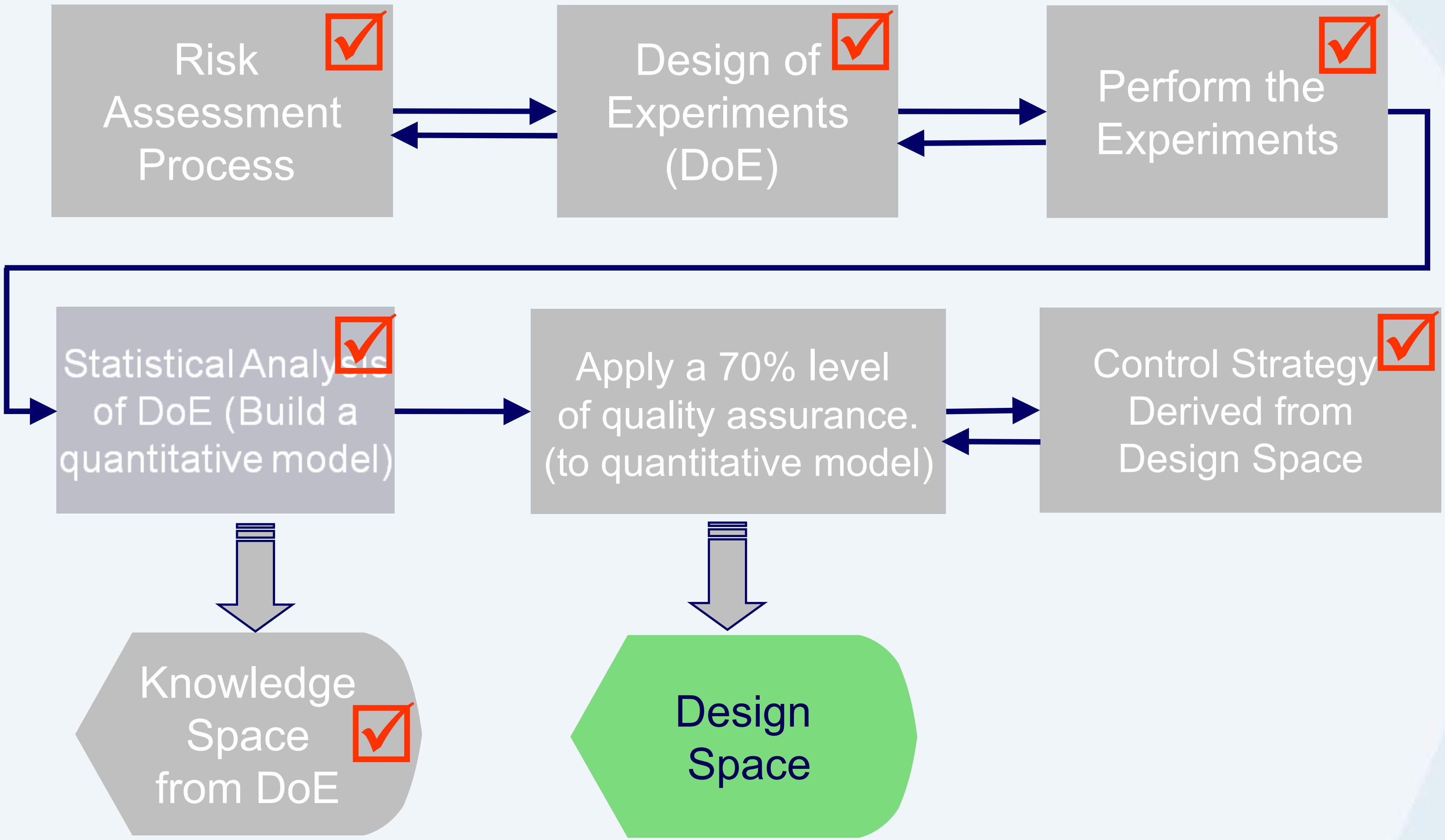
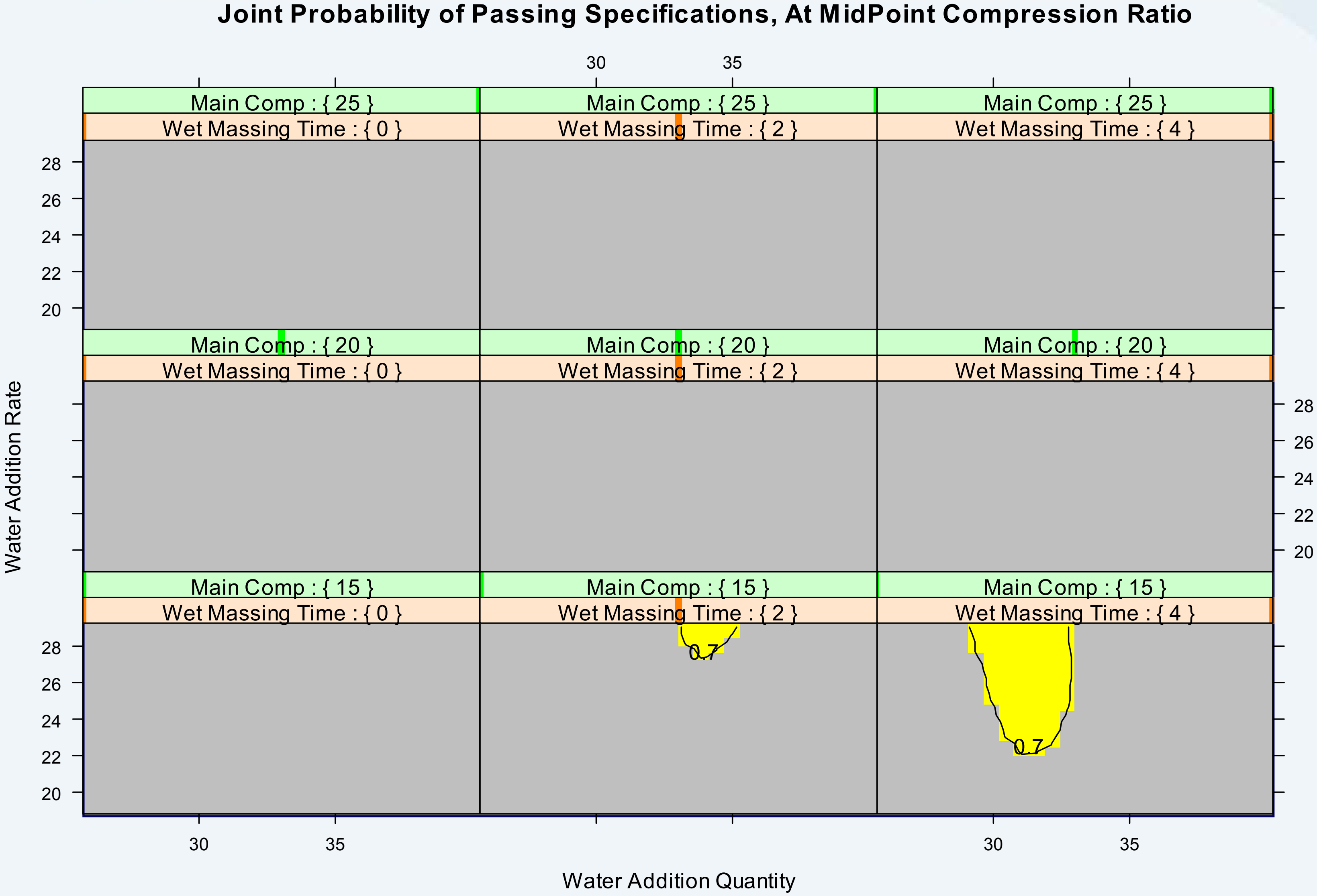


Example: OSD Granulation and Compression Design Space, with 1-α = 70%



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Questions?

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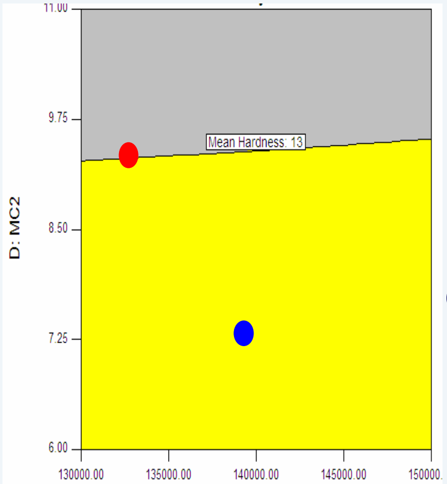
Backup Slides

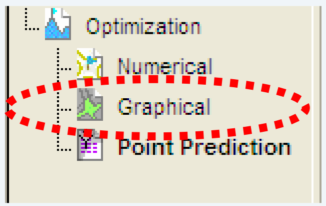
Design Expert Design Space Alternatives

Option A



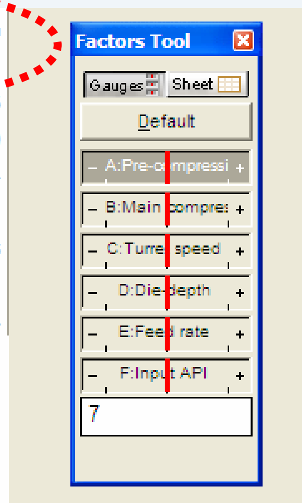
DX-7 Mocked example

- Yellow region is predicted pass, grey region is a fail.
- Red dot 50% probability of pass (univariate).
- Blue dot is >50% probability of pass, but do not know whether 50% or 99.9%

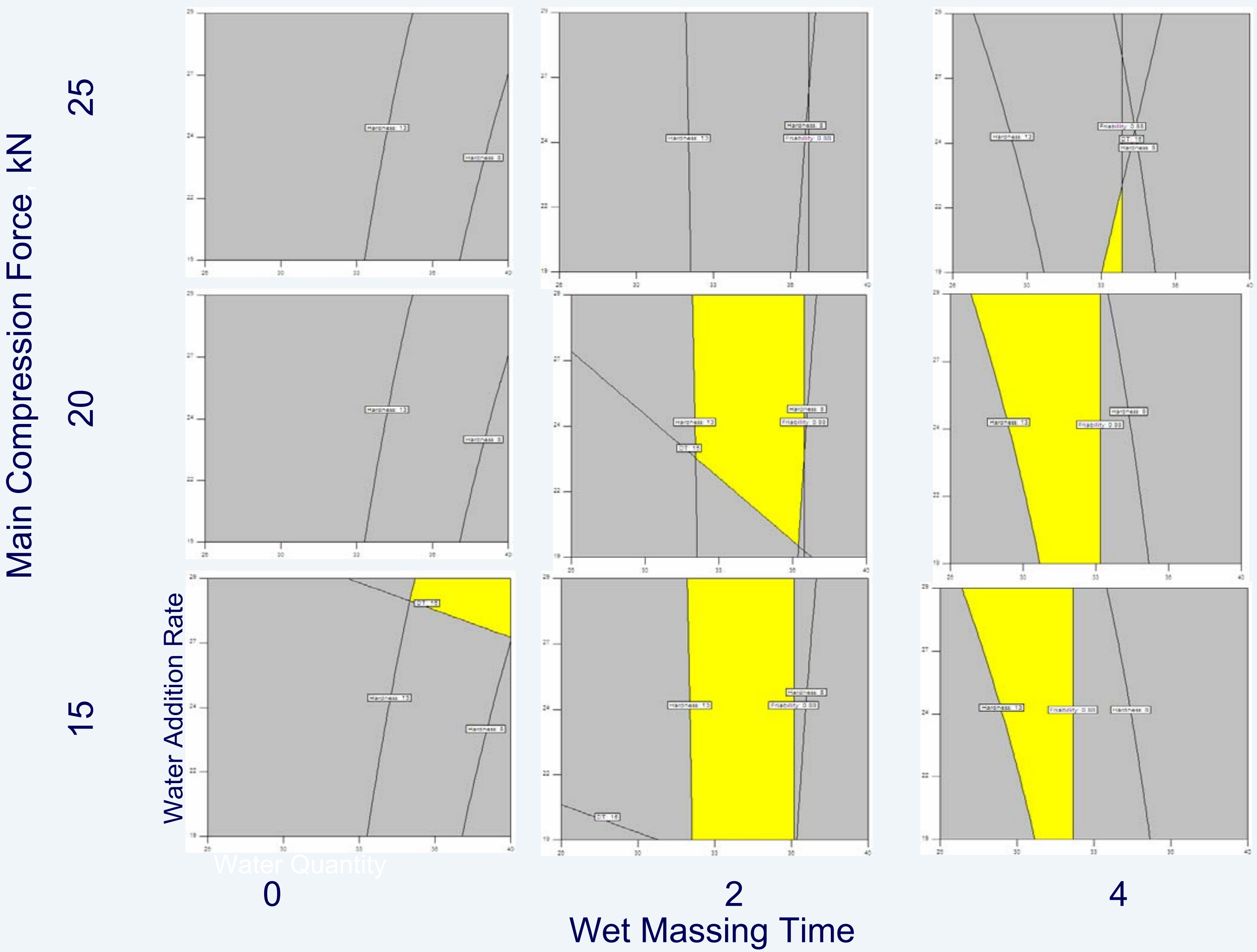


Option B

Response	Prediction	SE Mean	95% CI low	95% CI high	SE Pred	95% PI low	95% PI high
RSD on main compress	2.1		1.77	2.51		0.81	4.01
Process yield	98.9	0.54	97.85	100.03	3.83	91.23	106.65
Tablet weight variation	0.41		0.36	0.46		0.24	0.70
Tablet thickness	7.61	3.433E-003	7.60	7.61	0.018	7.57	7.64
Tablet thickness variatic	not analyzed	not analyzed	not analyzed	not analyzed	not analyzed	not analyzed	not analyzed
Tablet hardness	21.0	0.16	20.69	21.33	0.42	20.16	21.86
Tablet hardness variatic	not analyzed	not analyzed	not analyzed	not analyzed	not analyzed	not analyzed	not analyzed
T50	6.6	0.24	6.09	7.07	1.35	3.82	9.34

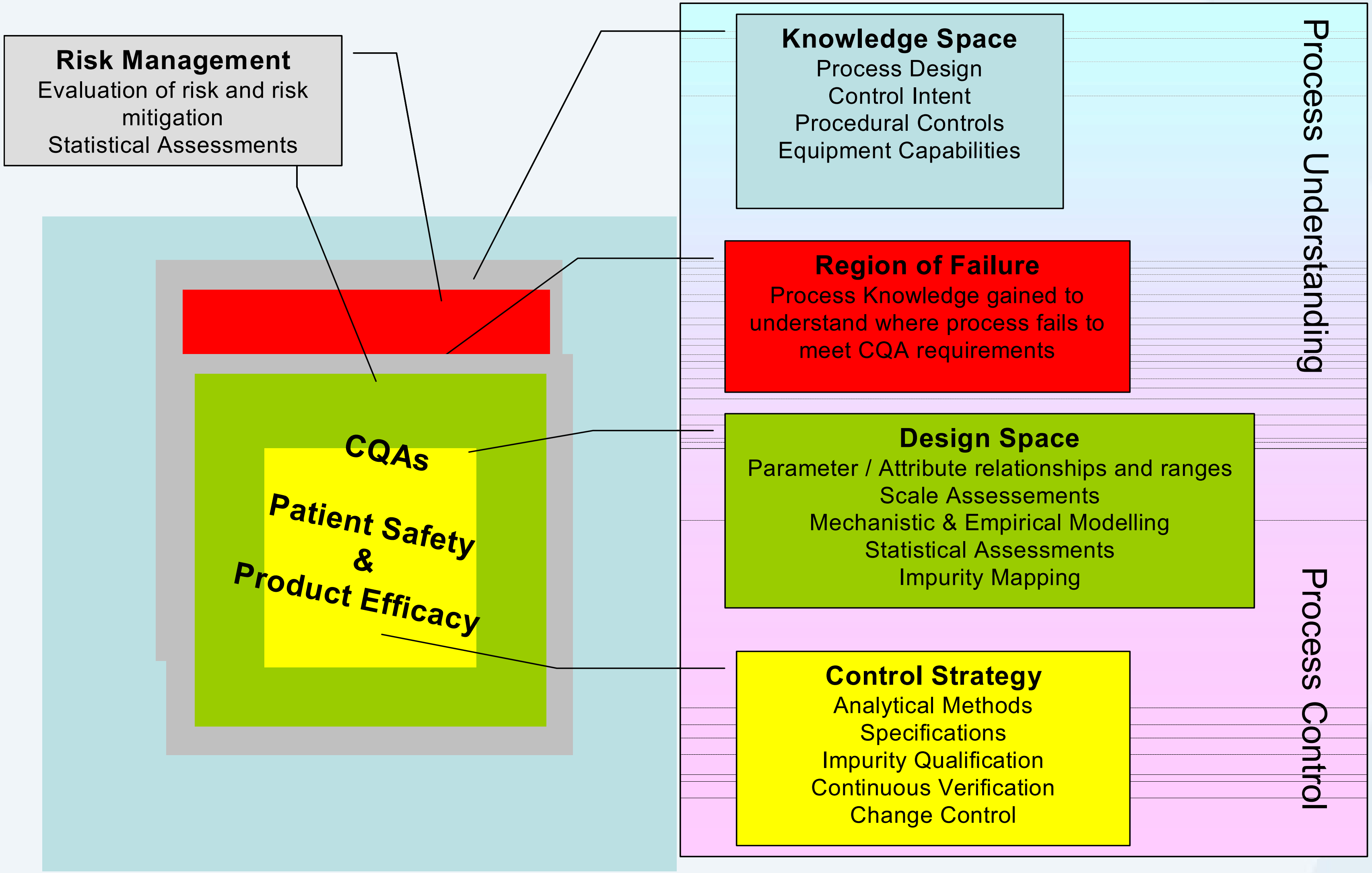


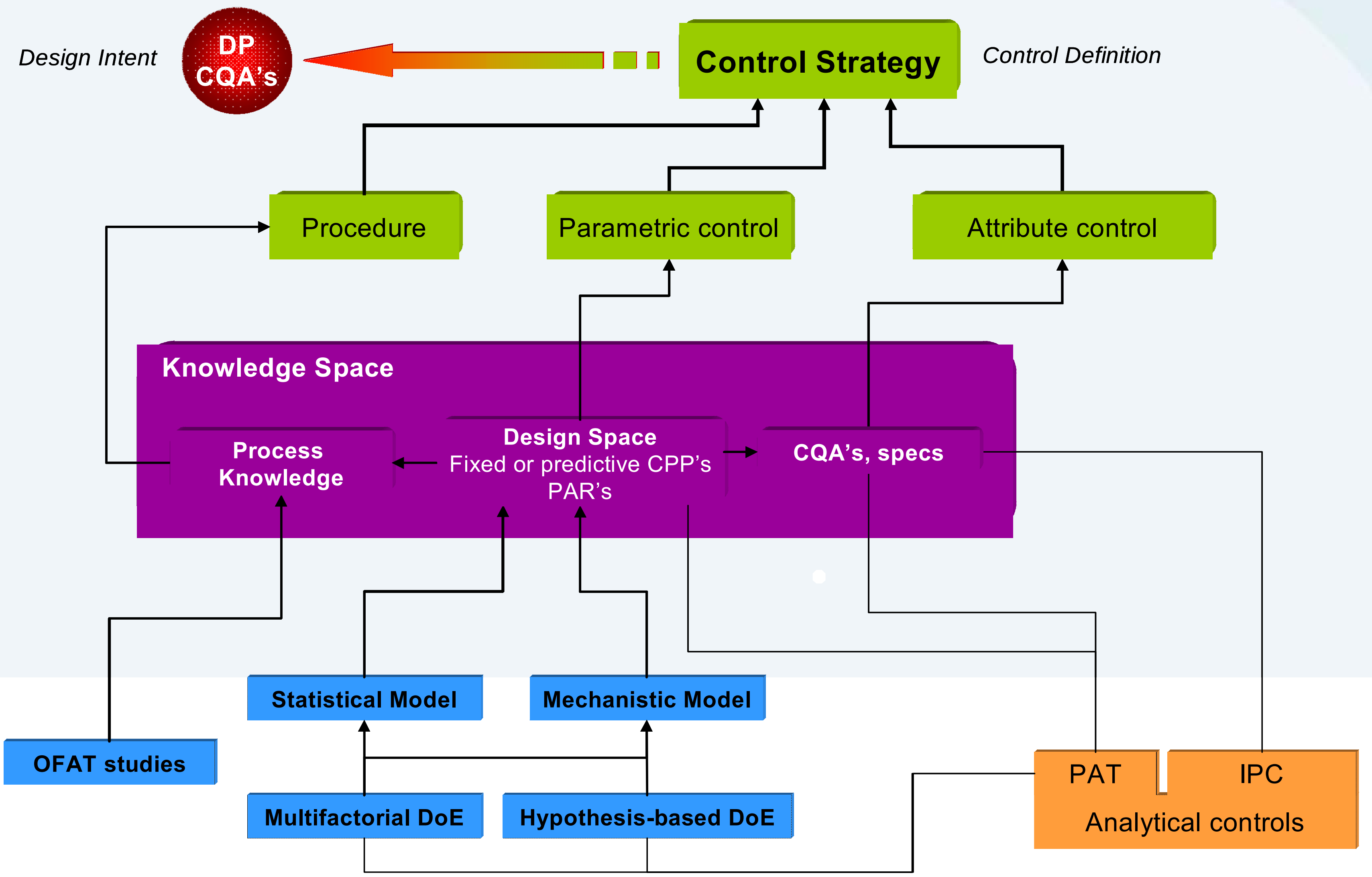
Example: OSD Granulation and Compression Design Space, Overlaying Means Approach



Mid point

Pre-comp ratio


Risk Management
Evaluation of risk and risk mitigation
Statistical Assessments
Knowledge Space
Process Design
Control Intent
Procedural Controls
Equipment Capabilities
Region of Failure
Process Knowledge gained to understand where process fails to meet CQA requirements
Design Space
Parameter / Attribute relationships and ranges
Scale Assessments
Mechanistic & Empirical Modelling
Statistical Assessments
Impurity Mapping
Control Strategy
Analytical Methods
Specifications
Impurity Qualification
Continuous Verification
Change Control
CQAs
Patient Safety
&
Product Efficacy
Process Understanding
Process Control


Design Intent
DP
CQA's
Control Strategy
Control Definition
Procedure
Parametric control
Attribute control
Knowledge Space
Process
Knowledge
Design Space
Fixed or predictive CPP's
PAR's
CQA's, specs
Statistical Model
Mechanistic Model
OFAT studies
Multifactorial DoE
Hypothesis-based DoE
PAT
IPC
Analytical controls