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Applicazione di tools QbD allo sviluppo e convalida di farmaci

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APTUIT VERONA

Agenda

- ✓ Cos'è il QbD?
- ✓ Classificazione dei modelli QbD secondo ICH Quality Working Group
- ✓ QbD Flow chart n°1 – *Early Development per un principio attivo BCS II*
- ✓ QbD Flow chart n°2 – *Development for Bioequivalence per un principio attivo BCS I (generico)*

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What is QbD?

It could be defined as a MULTISTEP process which starts with a ***Risk Identification & Evaluation*** step (1), then goes through a ***multivariate analisys*** (2,3) of product and process (product understanding) to reach a complete control strategy (3) during the product's lifecycle.

Basically, it consists on the following packages of techniques:

1. ***Risk Analysis tools***: qualitative and/or quantitative methodologies to screen factors/parameters/components/equipments which could have a potential influence on product (safety , efficacy and quality).

2. ***Active Multivariate statistical tools***: applied during a *development phase*, they enable to design and select the lower number of trials in order to gain the largest amount of information (DoEs, Mixture Design, RSM, etc..)

3. ***Passive Multivariate statistical tools***: using a large set of available data (*process/product hystorical data*) they can help finding the empirical model 'behind' a system, correlating process parameters and quality specifications (PCA, PLS, PLS-DA, etc..)

Except for point 1 , these methodologies belong to ***CHEMOMETRICS***

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La classificazione dei modelli QbD in funzione dell'intended use:

DA: ICH QUALITY IWG: POINTS TO CONSIDER FOR ICH Q8/Q9/Q10 IMPLEMENTATION

Some examples of different categories based on intended use are:

- *Models for supporting process design:*

  This category of models includes (but is not limited to) models for: formulation optimisation, process optimisation (e.g., reaction kinetics model), design space determination and scale-up. Models within this category can have different levels of impact. For example, a model for design space determination would generally be considered a medium-impact model, while a model for formulation optimisation would be considered a low-impact model.

- *Models for supporting analytical procedures:*

  In general, this category includes empirical (i.e., chemometric) models based on data generated by various Process Analytical Technology (PAT)-based methods, for example a calibration model associated with a near infrared (NIR)-based method. Models for supporting analytical procedures can have various impacts depending on the use of the analytical method. For example, if the method is used for release testing, then the model will be high-impact.

- *Models for process monitoring and control:*

  This category includes, but is not limited to:

  - *Univariate Statistical Process Control (SPC) or Multivariate Statistical Process Control (MSPC) based models:*

    These models are used to detect special cause variability; the model is usually derived and the limits are determined using batches manufactured within the target conditions. If an MSPC model is used for continuous process verification along with a traditional method for release testing, then the MSPC model would likely be classified as a medium-impact model. However, if an MSPC model is used to support a surrogate for a traditional release testing method in an RTRT approach, then the model would likely be classified as a high-impact model.

  - *Models used for process control (e.g., feed forward or feedback):*

Modelli ATTIVI per il Process Design:
-Se applicati per l'ottimizzazione di formula o processo = LOW IMPACT
- Se applicati per creare un DS trasferibile = MEDIUM IMPACT

[Elevato scientific understanding, Requirements di registrazione sostenibili = APPROCCIO ROUTINARIO]

Modelli PASSIVI di Supporto alle procedure analitiche o di Process Monitoring
-Se applicati NON in sostituzione di un end-product release testing – MEDIUM IMPACT
-Se applicati IN SOSTITUZIONE (SURROGATE) di un end-product release testing – HIGH IMPACT

[Elevato scientific understanding, Risparmio di tempi e costi con pari qualità, Requirements di validazione e registrazione complessi = APPROCCIO CASE BY CASE]

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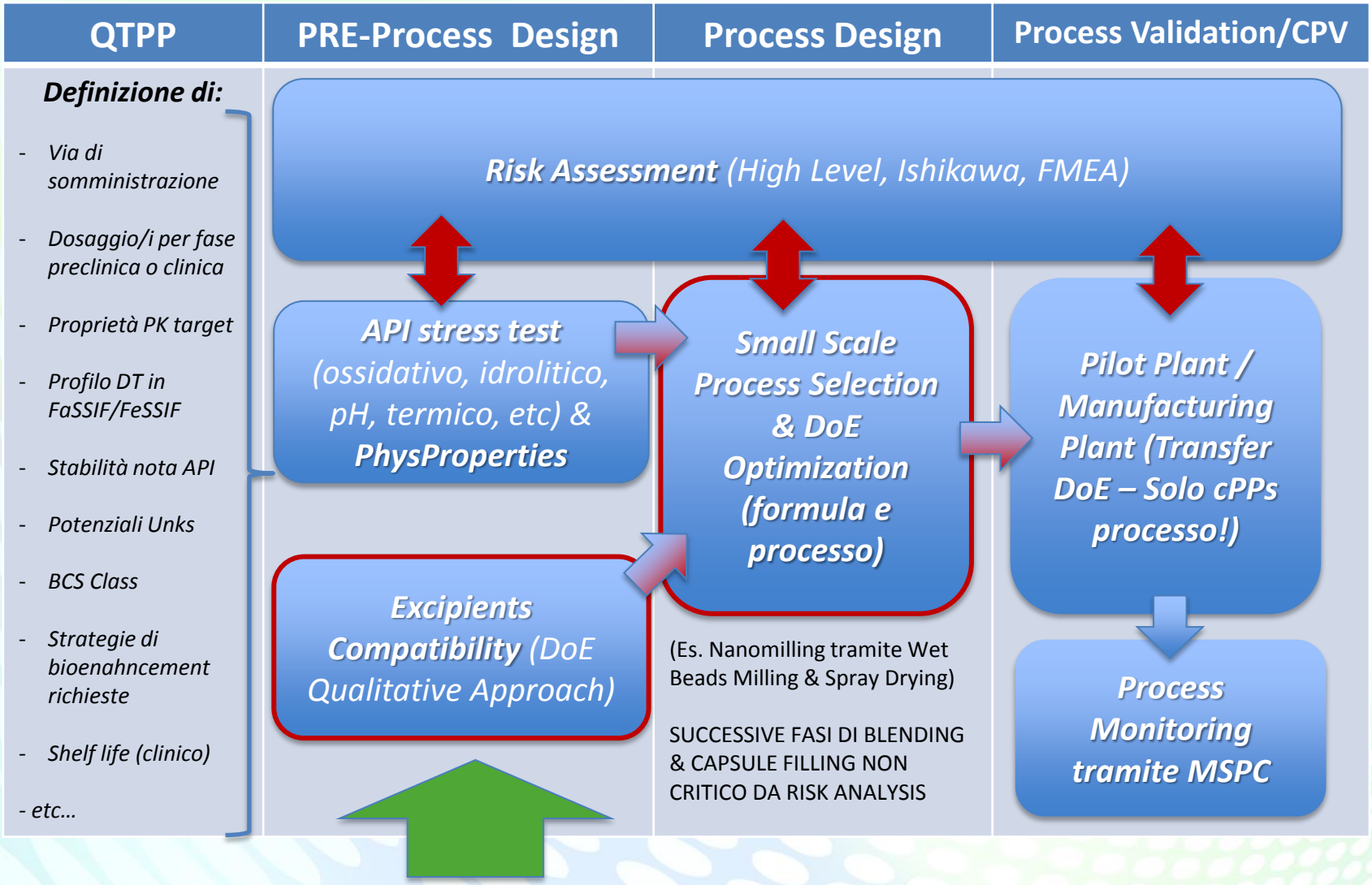
QbD approach n°1 – Early Development per un BCS II – (Bio-enhancement)



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Excipients Compatibility (qualitative approach)

Select	Std	Run	Factor 1 A:Nano-Poly...	Factor 2 B:Nano-Surf...	Factor 3 C:Bulking Ag...	Factor 4 D:Filler	Factor 5 E:Lubricant	Factor 6 F:Glidant	Factor 7 G:Antifoam/...	Factor 8 H:Disgregant	Response 1 API Known1	Response 2 API Known2	Response 3 API Unk3	Response 4 API Unk4	Response 5 API Unk5
	6	1	Hypromellose	Tween 80	Pearlitol	Lactose	Compritol 888 ATO	Aerosil 200	TPGS	Ac Di Sol	0	0.055	0	0.08	0
	12	2	Kollidon K30	SLS	Sucrose	Lactose	Compritol 888 ATO	None	TPGS	Ac Di Sol	0	0.58	0	0.12	0
	9	3	Kollidon K30	Tween 80	Sucrose	Avicel PH101	Mg Stearate	Aerosil 200	TPGS	Ac Di Sol	0	0.18	0	0.15	0
	13	4	Kollidon K30	Tween 80	Pearlitol	Lactose	Mg Stearate	None	TPGS	Glycolys	0	0.22	0	0.1	0
	7	5	Hypromellose	SLS	Pearlitol	Avicel PH101	Mg Stearate	None	TPGS	Ac Di Sol	0	0.98	0	0.12	0
	10	6	Kollidon K30	SLS	Pearlitol	Avicel PH101	Compritol 888 ATO	Aerosil 200	TPGS	Glycolys	0	0.65	0	0.11	0
	8	7	Kollidon K30	SLS	Pearlitol	Lactose	Mg Stearate	Aerosil 200	Simeticone	Ac Di Sol	0	1.02	0	0.25	0
	4	8	Hypromellose	Tween 80	Pearlitol	Avicel PH101	Mg Stearate	Aerosil 200	Simeticone	Glycolys	0	0.15	0	0.18	0
	1	9	Hypromellose	SLS	Pearlitol	Lactose	Compritol 888 ATO	None	Simeticone	Glycolys	0	0.55	0	0.15	0
	14	10	Kollidon K30	SLS	Sucrose	Avicel PH101	Mg Stearate	None	Simeticone	Glycolys	0	0.94	0	0.28	0
	15	11	Kollidon K30	Tween 80	Sucrose	Lactose	Compritol 888 ATO	Aerosil 200	Simeticone	Glycolys	0	0.062	0	0.3	0
	3	12	Hypromellose	SLS	Sucrose	Lactose	Mg Stearate	Aerosil 200	TPGS	Glycolys	0	0.9	0	0.08	0
	2	13	Hypromellose	Tween 80	Sucrose	Lactose	Mg Stearate	None	Simeticone	Ac Di Sol	0	0.17	0	0.14	0
	16	14	Hypromellose	Tween 80	Sucrose	Avicel PH101	Compritol 888 ATO	None	TPGS	Glycolys	0	0.044	0	0.07	0
	11	15	Kollidon K30	Tween 80	Pearlitol	Avicel PH101	Compritol 888 ATO	None	Simeticone	Ac Di Sol	0	0.066	0	0.27	0
	5	16	Hypromellose	SLS	Sucrose	Avicel PH101	Compritol 888 ATO	Aerosil 200	Simeticone	Ac Di Sol	0	0.6	0	0.1	0

8 Factors: A, B, C, D, E, F, G, H

Design Matrix Evaluation for Factorial 2FI Model

Factorial Effects Aliases

Est. Terms] Aliased Terms

[Intercept] = Intercept
[A] = A
[B] = B
[C] = C
[D] = D
[E] = E
[F] = F
[G] = G
[H] = H
[AB] = AB - CF - DH - EG
[AC] = AC - BF + DE + GH
[AD] = AD - BH + CE + FG
[AE] = AE - BG + CD + FH
[AF] = AF - BC + DG + EH
[AG] = AG - BE + CH + DF
[AH] = AH - BD + CG + EF

Il disegno selezionato e' un ***Min Res IV 2-level Fractional***. Perche?

- E' una matrice che mantiene una adeguata risoluzione (IV) pur riducendo notevolmente il n° di runs necessarie
- Permette un'adeguata stima delle interazioni binarie tra eccipienti

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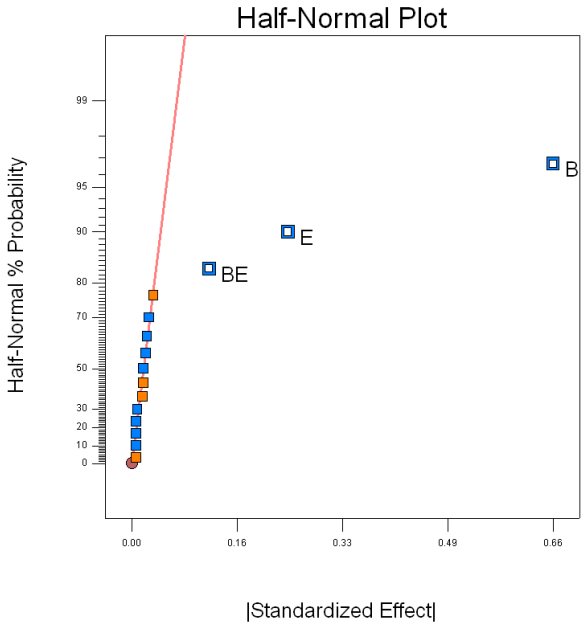
Excipient Compatibility – Response 2 (Known Degr.)

Design-Expert® Software
API Known2

Shapiro-Wilk test
W-value = 0.926
p-value = 0.340
A: Nano-Polymer
B: Nano-Surfactant
C: Bulking Agent
D: Filler
E: Lubricant
F: Glidant
G: Antifoam/Surfact
H: Disgregant
Positive Effects
Negative Effects



Response 2 API Known2

ANOVA for selected factorial model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	2.03	3	0.68	503.03	< 0.0001	significant
B-Nano-Surfa	*1.74*	*1*	*1.74*	*1288.94*	*< 0.0001*	
E-Lubricant	*0.24*	*1*	*0.24*	*176.82*	*< 0.0001*	
BE	*0.058*	*1*	*0.058*	*43.35*	*< 0.0001*	
Residual	0.016	12	1.348E-003			
Cor Total	2.05	15				

The Model F-value of 503.03 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case B, E, BE are significant model terms.

Values greater than 0.1000 indicate the model terms are not significant.

If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Std. Dev.	0.037	R-Squared	0.9921
Mean	0.45	Adj R-Squared	0.9901
C.V. %	8.20	Pred R-Squared	0.9860
PRESS	0.029	Adeq Precision	49.199

Final Equation in Terms of Coded Factors:

API Known2 =
+0.45
-0.33 * B
-0.12 * E
+0.060 * B * E

Final Equation in Terms of Actual Factors:

Nano-Surfactant SLS
Lubricant Mg Stearate
API Known2 =
+0.96000

Nano-Surfactant Tween 80
Lubricant Mg Stearate
API Known2 =
+0.18000

Nano-Surfactant SLS
Lubricant Compritol 888 ATO
API Known2 =
+0.59500

Nano-Surfactant Tween 80
Lubricant Compritol 888 ATO
API Known2 =
+0.056750

Vista l'assenza di Center Points, il 'noise' (Residual) e' calcolato con il metodo di Daniel (Effetto Hidden Replication)

Il modello e' adeguato in calibrazione ed in validazione (Internal Set)

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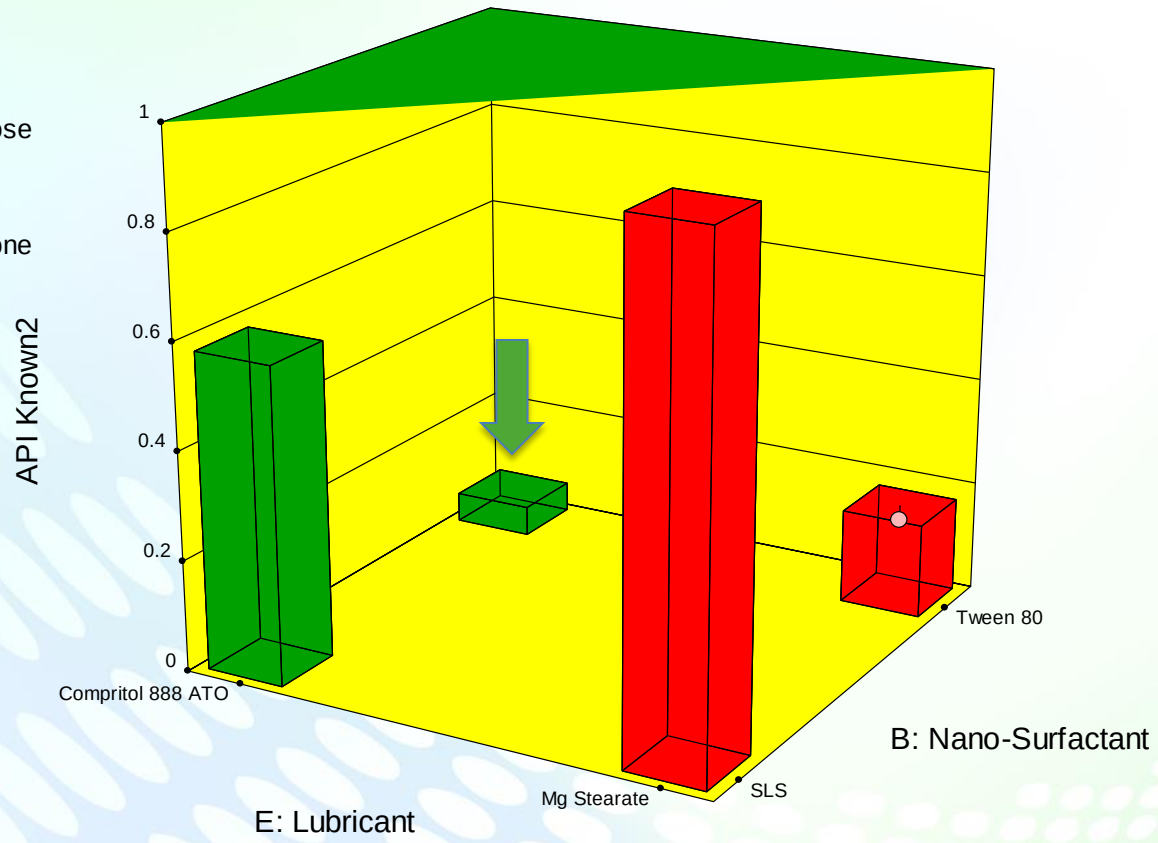
Excipient Compatibility – Response 2 (Known Degr.)

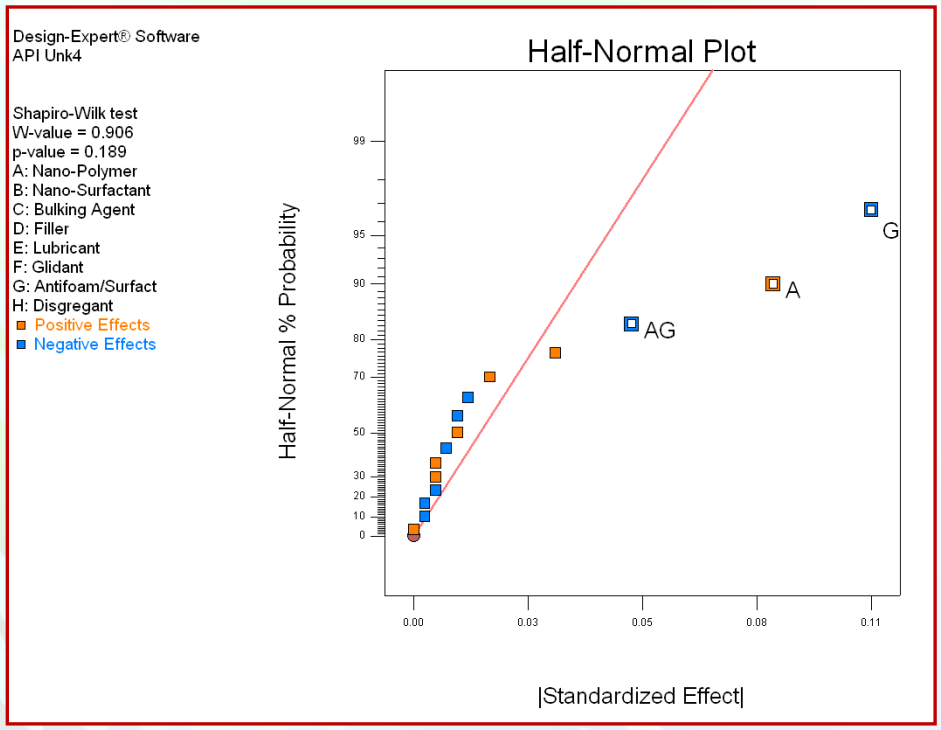
Design-Expert® Software
Factor Coding: Actual
API Known2
Design points below predicted value

X1 = B: Nano-Surfactant
X2 = E: Lubricant

Actual Factors
A: Nano-Polymer = Hypromellose
C: Bulking Agent = Pearlitol
D: Filler = Avicel PH101
F: Glidant = Aerosil 200
G: Antifoam/Surfact = Simeticone
H: Disgregant = Glycolys



Excipient Compatibility – Response 4 (Unknown Degr.)



Response 4 API Unk4

ANOVA for selected factorial model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	0.081	3	0.027	43.66	< 0.0001	significant
A-Nano-Poly.	*0.027*	*1*	*0.027*	*43.85*	*< 0.0001*	
G-Antifoam/S.	*0.044*	*1*	*0.044*	*71.03*	*< 0.0001*	
AG	*1.000E-002*	*1*	*1.000E-002*	*16.11*	*0.0017*	
Residual	7.450E-003	12	6.208E-004			
Cor Total	0.089	15				

The Model F-value of 43.66 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant.

In this case A, G, AG are significant model terms.

Values greater than 0.1000 indicate the model terms are not significant.

If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Std. Dev.	0.025	R-Squared	0.9161
Mean	0.16	Adj R-Squared	0.8951
C.V. %	15.95	Pred R-Square	0.8508
PRESS	0.013	Adeq Precisior	15.050

Final Equation in Terms of Coded Factors:

API Unk4 =
+0.16
+0.041 * A
-0.053 * G
-0.025 * A * G

Final Equation in Terms of Actual Factors:

Nano-Polymer Hypromellose
Antifoam/Surfact Simeticone
API Unk4 =
+0.14250

Nano-Polymer Kollidon K30
Antifoam/Surfact Simeticone
API Unk4 =
+0.27500

Nano-Polymer Hypromellose
Antifoam/Surfact TPGS
API Unk4 =
+0.087500

Nano-Polymer Kollidon K30
Antifoam/Surfact TPGS
API Unk4 =
+0.12000

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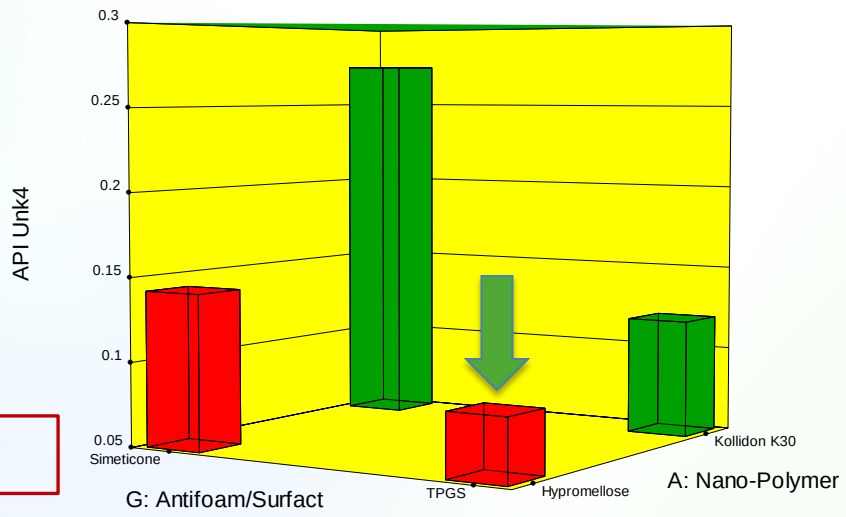
Excipient Compatibility – Response 4 (Unknown Degr.)

Design-Expert® Software
Factor Coding: Actual
API Unk4

X1 = G: Antifoam/Surfact
X2 = A: Nano-Polymer

Actual Factors
B: Nano-Surfactant = SLS
C: Bulking Agent = Pearlitol
D: Filler = Avicel PH101
E: Lubricant = Mg Stearate
F: Glidant = Aerosil 200
H: Disgregant = Glycolys

Resp.4 – 3D Analysis



La Desirability Function ottimizza simultaneamente le due funzioni di trasferimento verso le specifiche da noi richieste (in questo caso due, Risp2 e Risp.4)

Desirability Function (Resp.2+Resp.4)

Solutions for 16 combinations of categoric factor levels

Number	Nano-Polyme	Nano-Surfact	Bulking Agen	Filler	Lubricant	Glidant	Antifoam/Sur	Disgregant	API Known2	API Unk4	Desirability	
1	Hypromellose	Tween 80	Pearlitol	Avicel PH101	Compritol 888 A	Aerosil 200	TPGS	Glycolys	0.05675	0.0875	0.955	Selected
2	Hypromellose	Tween 80	Pearlitol	Avicel PH101	Mg Stearate	Aerosil 200	TPGS	Glycolys	0.18	0.0875	0.892	
3	Kollidon K30	Tween 80	Pearlitol	Avicel PH101	Compritol 888 A	Aerosil 200	TPGS	Glycolys	0.05675	0.12	0.879	
4	Hypromellose	Tween 80	Pearlitol	Avicel PH101	Compritol 888 A	Aerosil 200	Simeticone	Glycolys	0.05675	0.1425	0.822	
5	Kollidon K30	Tween 80	Pearlitol	Avicel PH101	Mg Stearate	Aerosil 200	TPGS	Glycolys	0.18	0.12	0.821	
6	Hypromellose	Tween 80	Pearlitol	Avicel PH101	Mg Stearate	Aerosil 200	Simeticone	Glycolys	0.18	0.1425	0.768	
7	Hypromellose	SLS	Pearlitol	Avicel PH101	Compritol 888 A	Aerosil 200	TPGS	Glycolys	0.595	0.0875	0.634	
8	Kollidon K30	SLS	Pearlitol	Avicel PH101	Compritol 888 A	Aerosil 200	TPGS	Glycolys	0.595	0.12	0.584	
9	Hypromellose	SLS	Pearlitol	Avicel PH101	Compritol 888 A	Aerosil 200	Simeticone	Glycolys	0.595	0.1425	0.546	
10	Kollidon K30	Tween 80	Pearlitol	Avicel PH101	Compritol 888 A	Aerosil 200	Simeticone	Glycolys	0.05675	0.275	0.328	
11	Kollidon K30	Tween 80	Pearlitol	Avicel PH101	Mg Stearate	Aerosil 200	Simeticone	Glycolys	0.18	0.275	0.306	
12	Hypromellose	SLS	Pearlitol	Avicel PH101	Mg Stearate	Aerosil 200	TPGS	Glycolys	0.96	0.0875	0.238	
13	Kollidon K30	SLS	Pearlitol	Avicel PH101	Mg Stearate	Aerosil 200	TPGS	Glycolys	0.96	0.12	0.219	
14	Kollidon K30	SLS	Pearlitol	Avicel PH101	Compritol 888 A	Aerosil 200	Simeticone	Glycolys	0.595	0.275	0.218	
15	Hypromellose	SLS	Pearlitol	Avicel PH101	Mg Stearate	Aerosil 200	Simeticone	Glycolys	0.96	0.1425	0.205	
16	Kollidon K30	SLS	Pearlitol	Avicel PH101	Mg Stearate	Aerosil 200	Simeticone	Glycolys	0.96	0.275	0.082	

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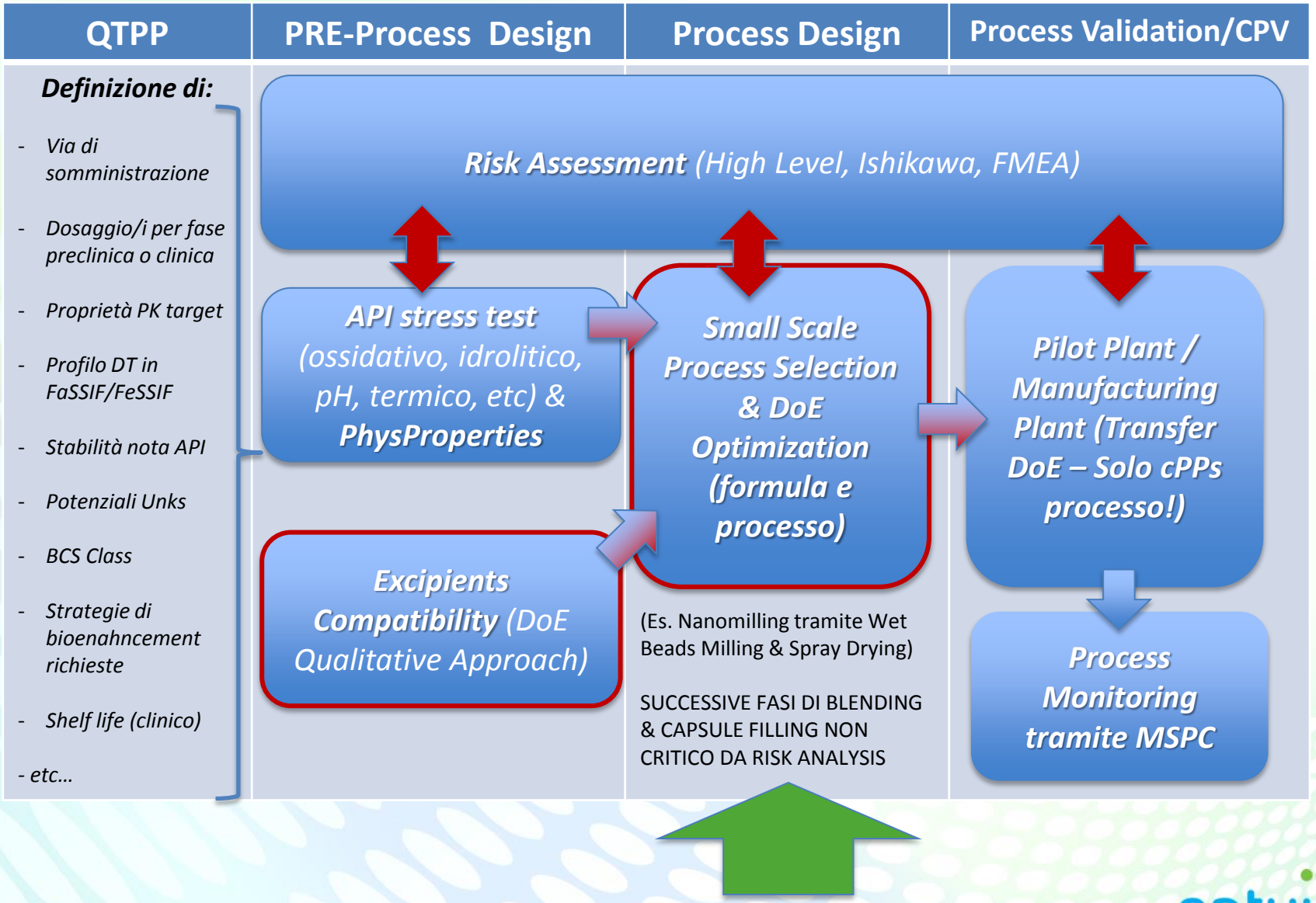
QbD approach n°1 – Early Development per un BCS II – (Bio-enhancement)



Process Design DoE (2-level FF Resolution IV)

	Name	Units	Type	Low	High
A [Numeric]	API amount	%	Numeric	5	15
B [Numeric]	HPMC amount	%	Numeric	4	8
C [Numeric]	Tween 80	%	Numeric	1	2
D [Numeric]	SD sol dilution		Numeric	1	2
E [Numeric]	Pump speed	g/min	Numeric	10	20
F [Numeric]	Atomization		Numeric	400	800
G [Numeric]	Inlet Temperature	°C	Numeric	110	130
H [Numeric]	Vacuum		Numeric	25	50

Si indagano 4 fattori di formulazione (nanosuspension, A-D) congiuntamente a 4 fattori di processo SD (E-H)

	Name	Units	Diff. to detect Delta("Signal")	Est. Std. Dev. Sigma("Noise")	Delta/Sigma (Signal/Noise Ratio)
	Sum degr. nanosusp 7 gg	%			
	PSD nanosusp t0	nm			
	PSD nanosup 7gg	nm			
	PSD dried powder	nm			
	Amount not crystalline form	%			
	PSD after redispersion	nm			
	Total Flowability Index				
	Bioril DT at 10 min	%			
	Bioril at end	%			

Si modellano 9 responses: le prime tre sono legate alle performance della nanosospensione, le successive a quelle della Dried Powder finale

Number of Factors

	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
4	2^{2}	2^{3-1} III													
8		2^{3}	2^{4-1} IV	2^{5-2} III	2^{6-3} III	2^{7-4} III									
16			2^{4}	2^{5-1} V	2^{6-2} IV	2^{7-3} IV	2^{8-4} IV	2^{9-5} III	2^{10-6} III	2^{11-7} III	2^{12-8} III	2^{13-9} III	2^{14-10} III	2^{15-11} III	
32				2^{5}	2^{6-1} VI	2^{7-2} IV	2^{8-3} IV	2^{9-4} IV	2^{10-5} IV	2^{11-6} IV	2^{12-7} IV	2^{13-8} IV	2^{14-9} IV	2^{15-10} IV	2
64					2^{6}	2^{7-1} VII	2^{8-2} V	2^{9-3} IV	2^{10-4} IV	2^{11-5} IV	2^{12-6} IV	2^{13-7} IV	2^{14-8} IV	2^{15-9} IV	2
128						2^{7}	2^{8-1} VIII	2^{9-2} VI	2^{10-3} V	2^{11-4} V	2^{12-5} IV	2^{13-6} IV	2^{14-7} IV	2^{15-8} IV	2
256							2^{8}	2^{9-1} IX	2^{10-2} VI	2^{11-3} VI	2^{12-4} VI	2^{13-5} V	2^{14-6} V	2^{15-7} V	2
512								2^{9}	2^{10-1} X	2^{11-2} VII	2^{12-3} VI	2^{13-4} VI	2^{14-5} VI	2^{15-6} VI	2

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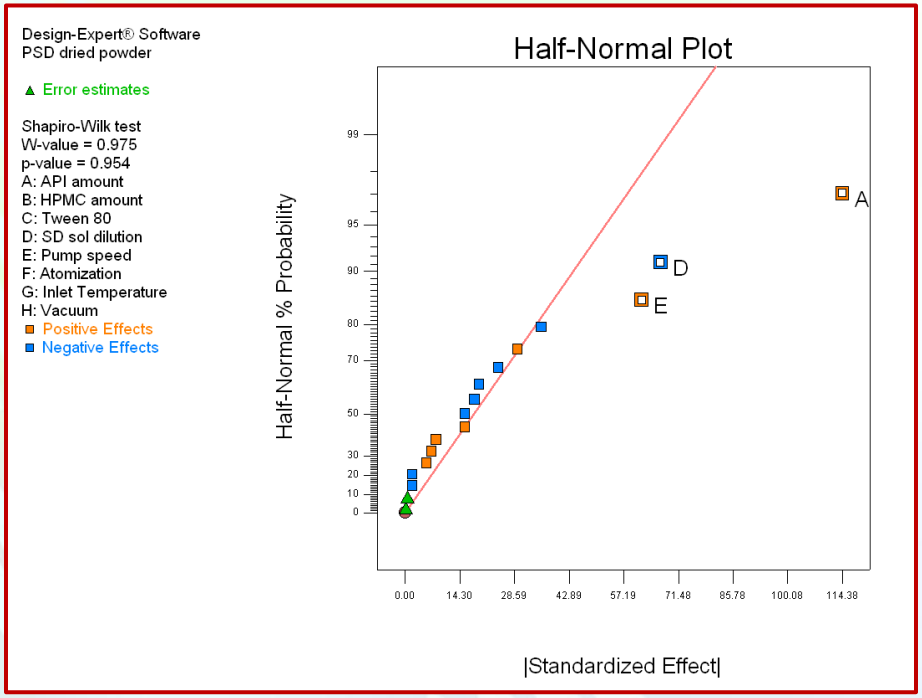
Response 4: PSD Dried powder



I Center Points fungono anche da check di linearita' del modello

ANOVA for selected factorial model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	85529.69	3	28509.90	24.22	< 0.0001	significant
A-API amoun	*52326.56*	*1*	*52326.56*	*44.45*	*< 0.0001*	
D-SD sol dilu	*17889.06*	*1*	*17889.06*	*15.20*	*0.0016*	
E-Pump spee	*15314.06*	*1*	*15314.06*	*13.01*	*0.0029*	
Curvature	2.22	1	2.22	1.886E-003	0.9660	not significant
Residual	16481.25	14	1177.23			
Lack of Fit	*16281.25*	*12*	*1356.77*	*13.57*	*0.0706*	*not significant*
Pure Error	*200.00*	*2*	*100.00*			
Cor Total	1.020E+005	18				

Essendo disponibili Center Points, il 'noise' e' calcolato come MS da tali punti (percio' DX lo definisce Pure Error). Il metodo di Daniel viene comunque usato per stimare I Residual (come in precedenza). La loro differenza matematica stima il LoF: in caso di valore significativo bisogna indagare meglio la selezione fatta sui cPPs

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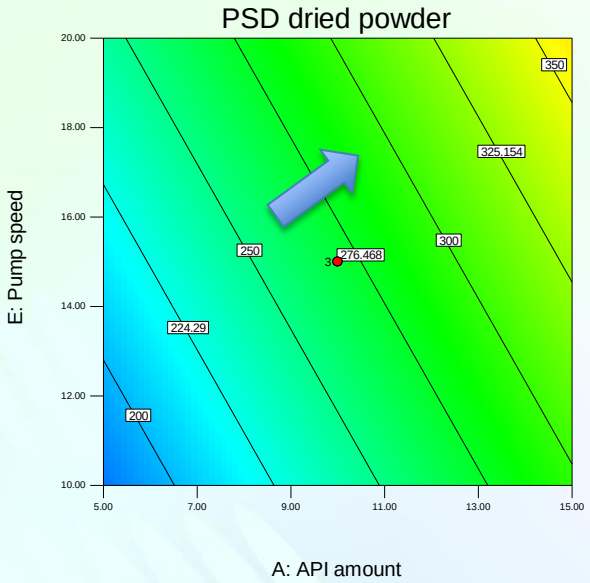
Response 4: PSD Dried powder, Contour plots

Design-Expert® Software
Factor Coding: Actual
PSD dried powder
Design Points
420
150

X1 = A: API amount
X2 = E: Pump speed

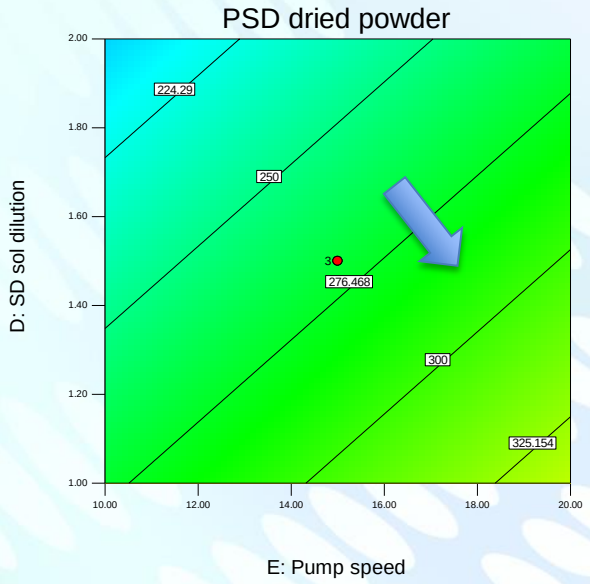
Actual Factors
B: HPMC amount = 6.00
C: Tween 80 = 1.50
D: SD sol dilution = 1.50
F: Atomization = 600.00
G: Inlet Temperature = 120.00
H: Vacuum = 37.50



Design-Expert® Software
Factor Coding: Actual
PSD dried powder
Design Points
420
150

X1 = E: Pump speed
X2 = D: SD sol dilution

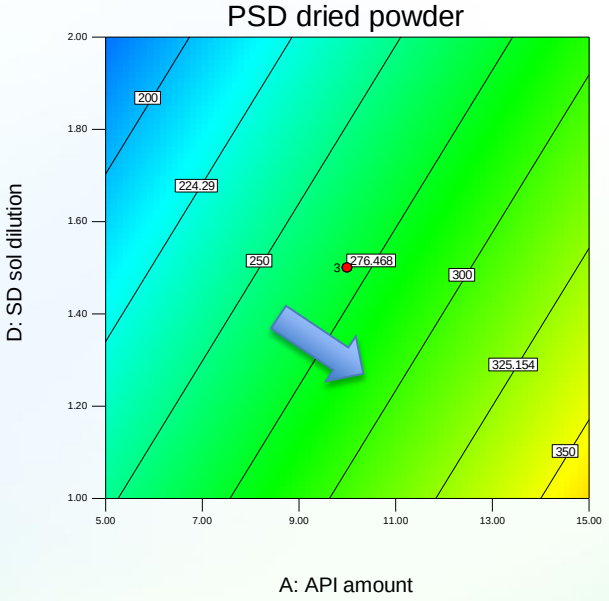
Actual Factors
A: API amount = 10.00
B: HPMC amount = 6.00
C: Tween 80 = 1.50
F: Atomization = 600.00
G: Inlet Temperature = 120.00
H: Vacuum = 37.50



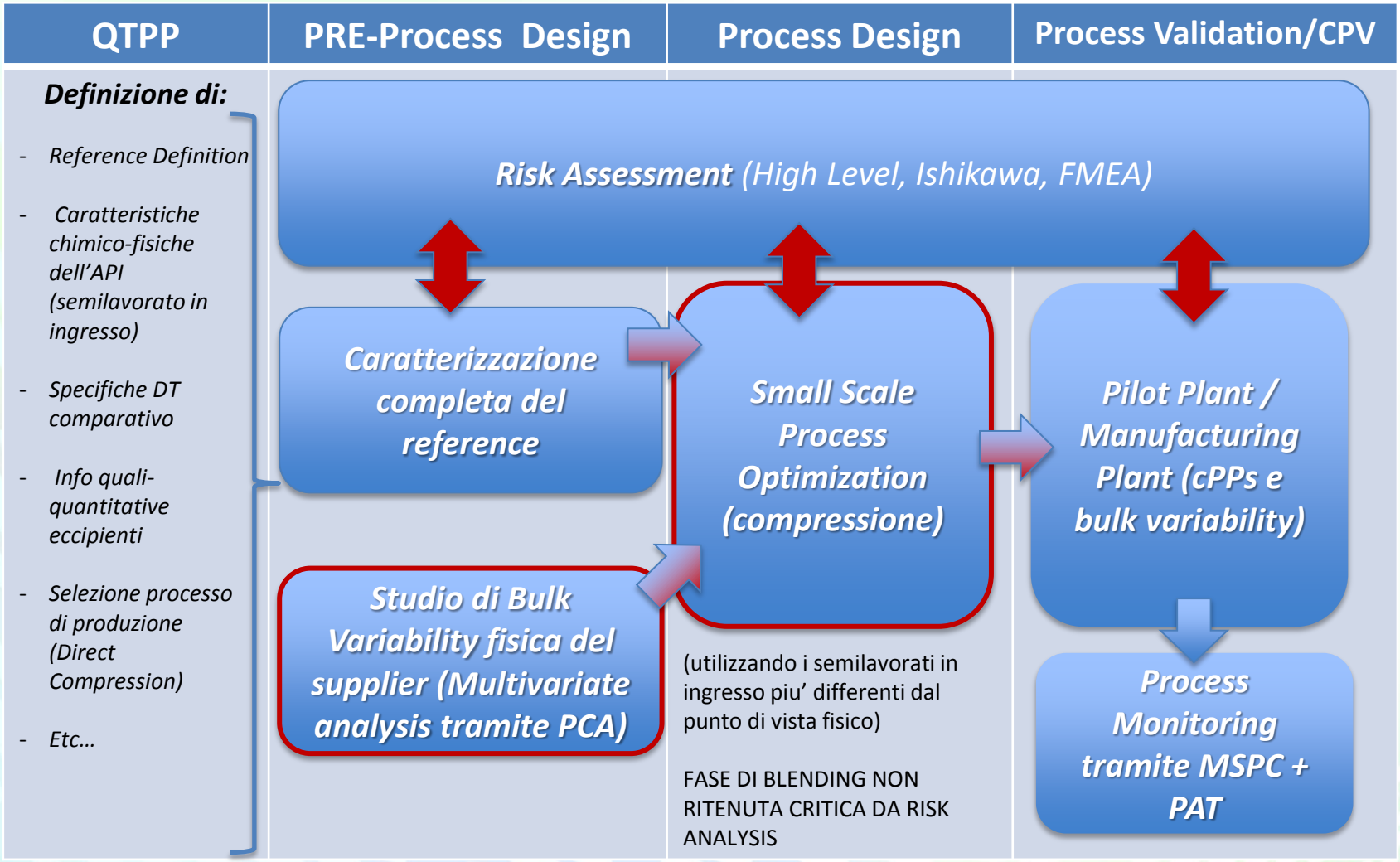
Design-Expert® Software
Factor Coding: Actual
PSD dried powder
Design Points
420
150

X1 = A: API amount
X2 = D: SD sol dilution

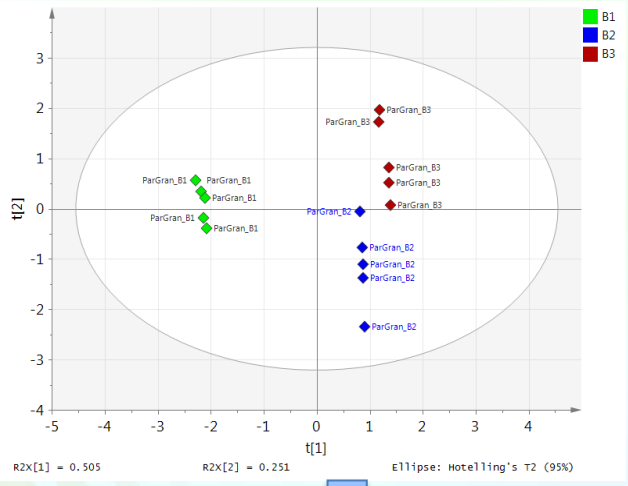
Actual Factors
B: HPMC amount = 6.00
C: Tween 80 = 1.50
E: Pump speed = 15.00
F: Atomization = 600.00
G: Inlet Temperature = 120.00
H: Vacuum = 37.50

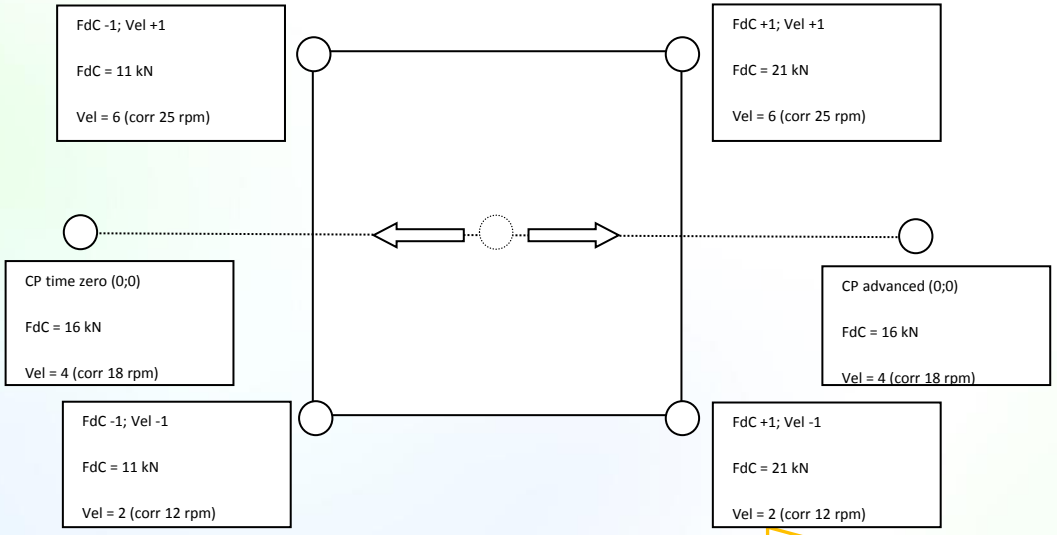


QbD approach n°2 – Development & Bioequivalence per un API BCS I



Bulk variability analysis & tabletting





Std	Run	Block	Factor 1 A:FdC kN	Factor 2 B:Vel rpm	Response 1 DT release 5' Minutes	Response 2 DT release 10' Minutes	Response 3 Mean Hardnes kP	Response 4 Mean Thicknes mm
10	1	Partita 001	21.00	25.00	71.7	91.6	10.76	5.86
1	2	Partita 001	11.00	11.00	79.4	94.2	5.26	6.14
13	3	Partita 001	16.00	18.00	74.1	92.8	8.8	5.94
4	4	Partita 001	21.00	11.00	73.2	93.2	11.32	5.88
7	5	Partita 001	11.00	25.00	77.8	92.8	5.53	6.11
14	6	Partita 001	16.00	18.00	76.2	92.7	9.1	5.94
5	7	Partita 002	21.00	11.00	72.9	92.1	12	5.88
16	8	Partita 002	16.00	18.00	78.1	92.2	8.92	5.96
8	9	Partita 002	11.00	25.00	77.2	91.9	5.87	6.12
11	10	Partita 002	21.00	25.00	72.6	91.4	12.17	5.83
2	11	Partita 002	11.00	11.00	75.5	92.7	6.26	6.12
15	12	Partita 002	16.00	18.00	72.2	91.9	9.88	5.96
18	13	Partita 003	16.00	18.00	75.1	92	9.33	5.95
3	14	Partita 003	11.00	11.00	76.9	93.5	6.2	6.12
6	15	Partita 003	21.00	11.00	71.3	92.2	12.02	5.84
12	16	Partita 003	21.00	25.00	72.6	91.1	11.5	5.86
17	17	Partita 003	16.00	18.00	74.6	91.7	9.52	5.94
9	18	Partita 003	11.00	25.00	76.3	92.4	6.25	6.11

Time / Batch lenght

Scale up (labo, pilota, industriale):

-20 Kg (Blending & Tabletting Labo)

- 200 Kg (Blending & Tabletting Pilota)

- 2000 Kg (Blending & Tabletting Industriale)

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Considerazioni

- Per ogni progetto (early, medium o late stage dev) e' utile costruire un flow chart delle macrofasi (QTPP, Pre-Process Design, Process Design, PV/CPV) in ottica QbD

- Adattando tale schema il flow chart puo' diventare *Phase-oriented (*preclinical, clinical phase I, II, III, Transfer and PV, Manufacturing)

- Tali fasi possono essere implementate con attivita' QbD associate ad altri dipartimenti (es. IVIVC per PK)

- Conoscere i tools QbD permette di 'riempire' tale flow chart con le metodogie piu' utili per lo specifico obbiettivo.

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Thank You.

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