How to improve quality and consistency of legacy products applying QbD/Six Sigma methodology. A Case Study.

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Departament de Salut
Direcció General de Regulació, Planificació i Recursos Sanitaris

Recomanacions per a l'aplicació de sistemes de gestió de la qualitat pel disseny (QbD) en la fabricació industrial de medicaments comercialitzats

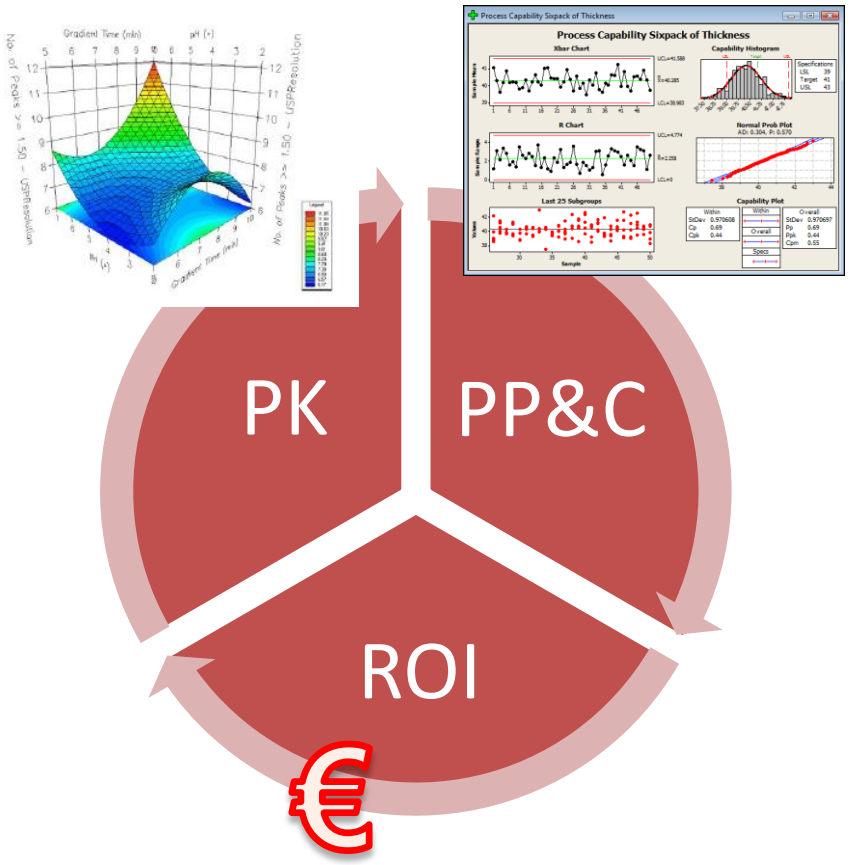
8 d'agost de 2014 (versió 1)

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QbD as an improvement methodology for pharmaceutical legacy products.

A Case study.

Working Team organization



Team members	
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Carles Cirera	President ISPE Spain

Project schedule

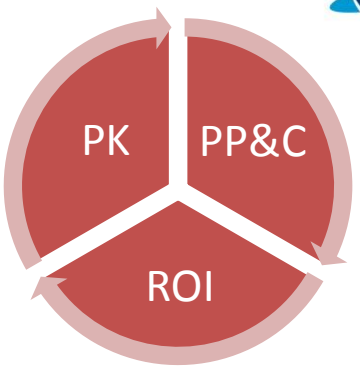
1. First meeting of the working group: 17/09/2012
2. Final full paper draft : November 2013
3. Reviews:
    1. Consistency of wording: (Catalan and English).
    2. Contents: by the Advisory Committee for Quality Assurance on industrialized medicinal products.

Paper available since September 2014





Project goals (1)



1. Identify industry professionals with different backgrounds: development, quality, regulatory, to discuss the implementation of QbD in the industry.
2. Incorporate the vision and the advice from the compliance and regulations (GMP inspectors).

Project goals (2)

1. Develop a working document describing:
    1. The **QbD method (and tools)** applied to the continuous improvement (ICH Q10)
    2. **A Case Study** as simple as possible to show that the use of QbD is not limited to development and does not have to be expensive and impracticable.
    3. How to calculate **the ROI of an improvement project**. The business case …

Questions to answer

1. How to prove that the processes are under control and what criteria will be applied in inspections?
2. How to "measure" the probability of nonconforming product?
3. What level of probability of nonconformance may be acceptable? And if it is not, how can you improve?
4. How to apply the concept of "continuous improvement" ICH Q10 and GMP Chapter 1?
5. How to calculate the ROI of an improvement project?

Key indicators of process performance

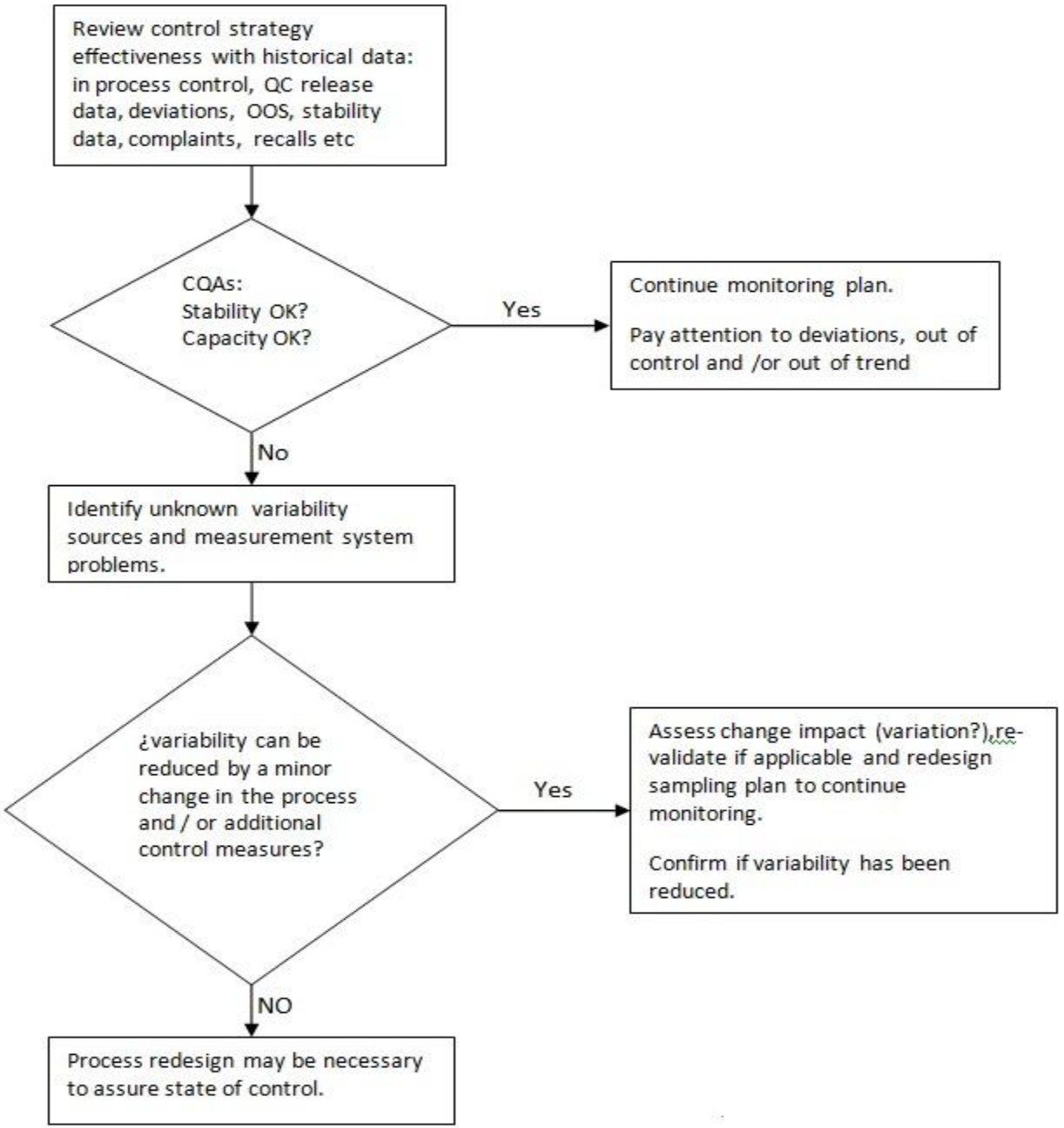


Table 2 Priority factors for QbD project selection

$$PC = FA \times FB \times FC \times FD$$

	Indicators	Priority Factors	Score
Product Quality	% batch non-conform / rejected	**Factor A** No-conformity	< 1%: score 1 1-5%: score 5 > 5%: score 10
	% deviations	**Factor B** Deviations	Non critical deviations: score 1 Critical deviations: score 1,2
Process Performance	Process capability	**Factor C** Ppk per CQA	Ppk ≤ 1, low capability: score 10 1 < Ppk < 1,3, medium capability: score 5 Ppk ≥ 1,3, high capability: score 1
Manufacturing Volume	Produced units/year	**Factor D** Millions units/year	< 0,5 : score 1 0,5-2 : score 5 > 2 : score 10

Table 3 Example of QbD project selection

Product	Sales (units)	Factor A (non conformity)	Factor B (deviations)	Factor C (Ppk)	Factor D (volume)	Score (AxBxCxD)	Priority
M	2.000.000	10	1	10	10	1.000	High
A	1.900.000	5	1,2	10	5	300	High
P	4.000.000	5	1	5	10	250	High
B	3.900.000	1	1	10	10	100	High
K	2.500.000	1	1	10	10	100	High
C	3.600.000	1	1,2	5	10	60	Medium
F	800.000	1	1,2	10	5	60	Medium
L	7.000.000	1	1,2	5	10	60	Medium
N	350.000	5	1,2	10	1	60	Medium
E	850.000	1	1	5	5	25	Medium
I	1.200.000	1	1	5	5	25	Medium
Q	300.000	5	1	5	1	25	Medium
S	45.000	5	1	5	1	25	Medium
G	2.500.000	1	1,2	1	10	12	Medium
R	75.000	1	1,2	10	1	12	Medium
T	15.000	1	1,2	10	1	12	Medium
O	700.000	1	1,2	1	5	6	Low
D	150.000	1	1	5	1	5	Low
H	500.000	1	1	1	5	5	Low
J	600.000	1	1	1	5	5	Low

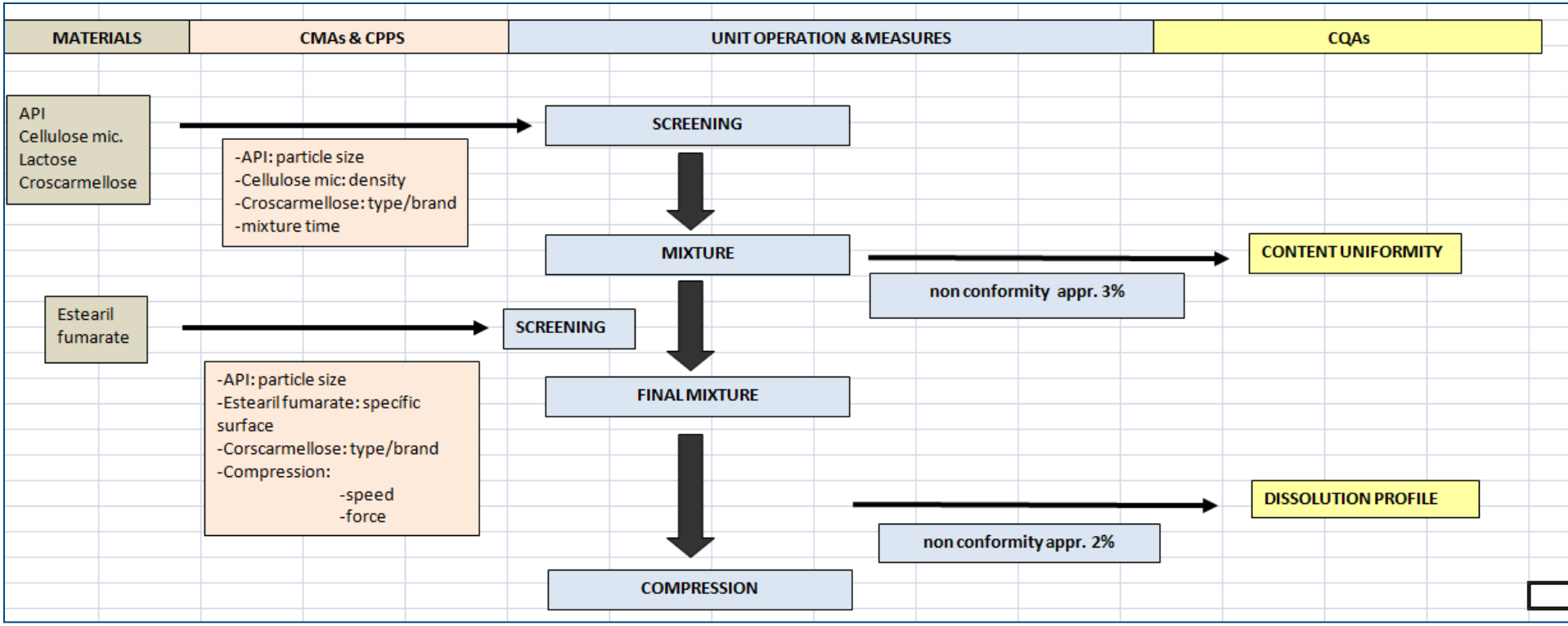
Document contents

1. **Chapter 1**: Introduction.
2. **Chapter 2:** Evaluation of the state of control of manufacturing processes, criteria and statistical tools to verify that the processes are stable and capable.
3. **Chapter 3:** Assessment of deficiencies in the design, and in the understanding of the manufacturing processes as well as an improvement proposal; criteria and tools to acquire the necessary knowledge of the process and to identify improvement actions and / or to redesign the process if necessary.

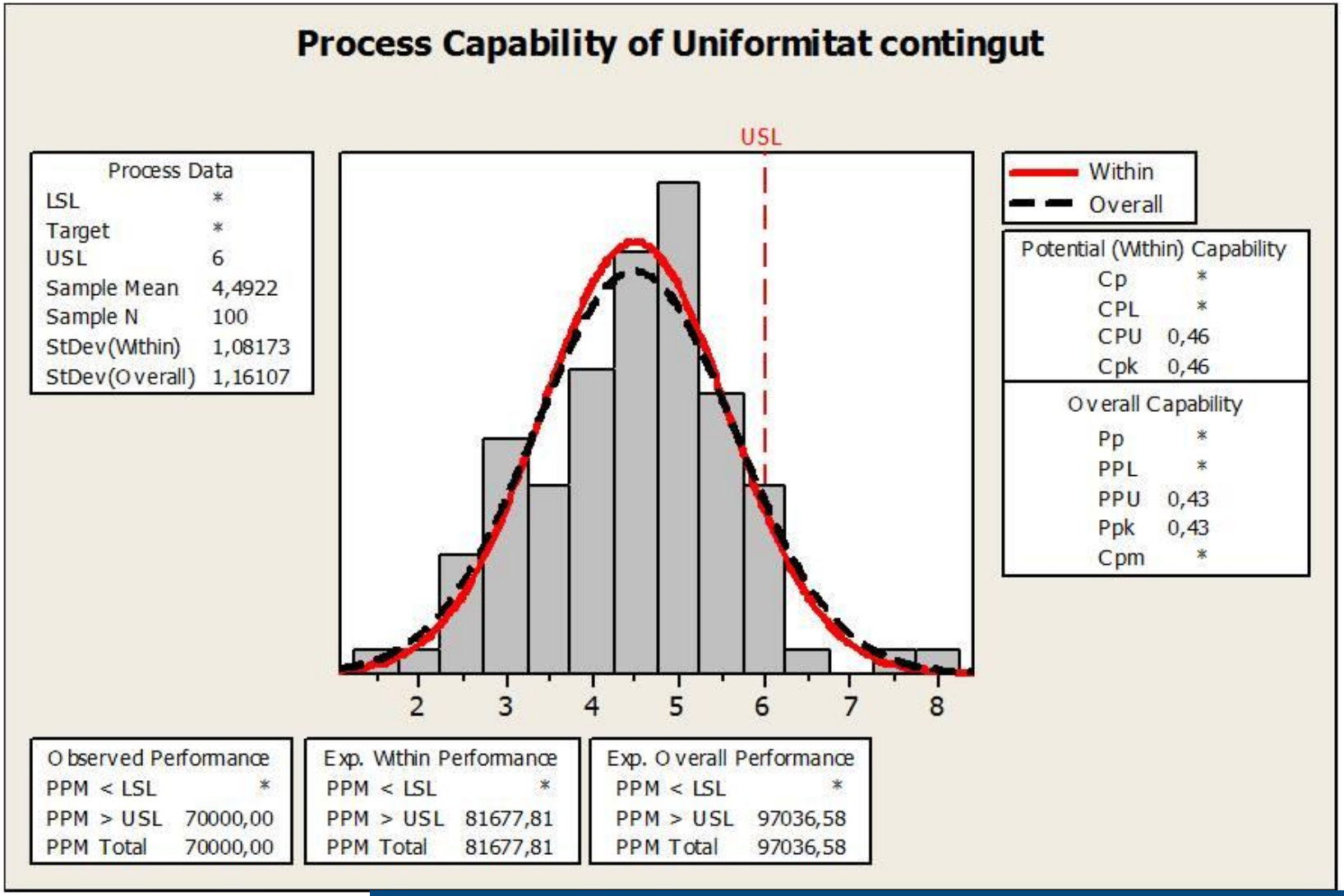
Document contents

4. **Chapter 4**: criteria for calculating the ROI of a project based on QbD; methodology to prioritize improvement projects and to calculate the necessary investment and savings estimations for each case.
5. **Chapter 5**: Case Study, application of the previous chapters to a fictitious example: improvement project in tablet manufacturing.
6. **Glossary of Terms**.

The process & the quality problem

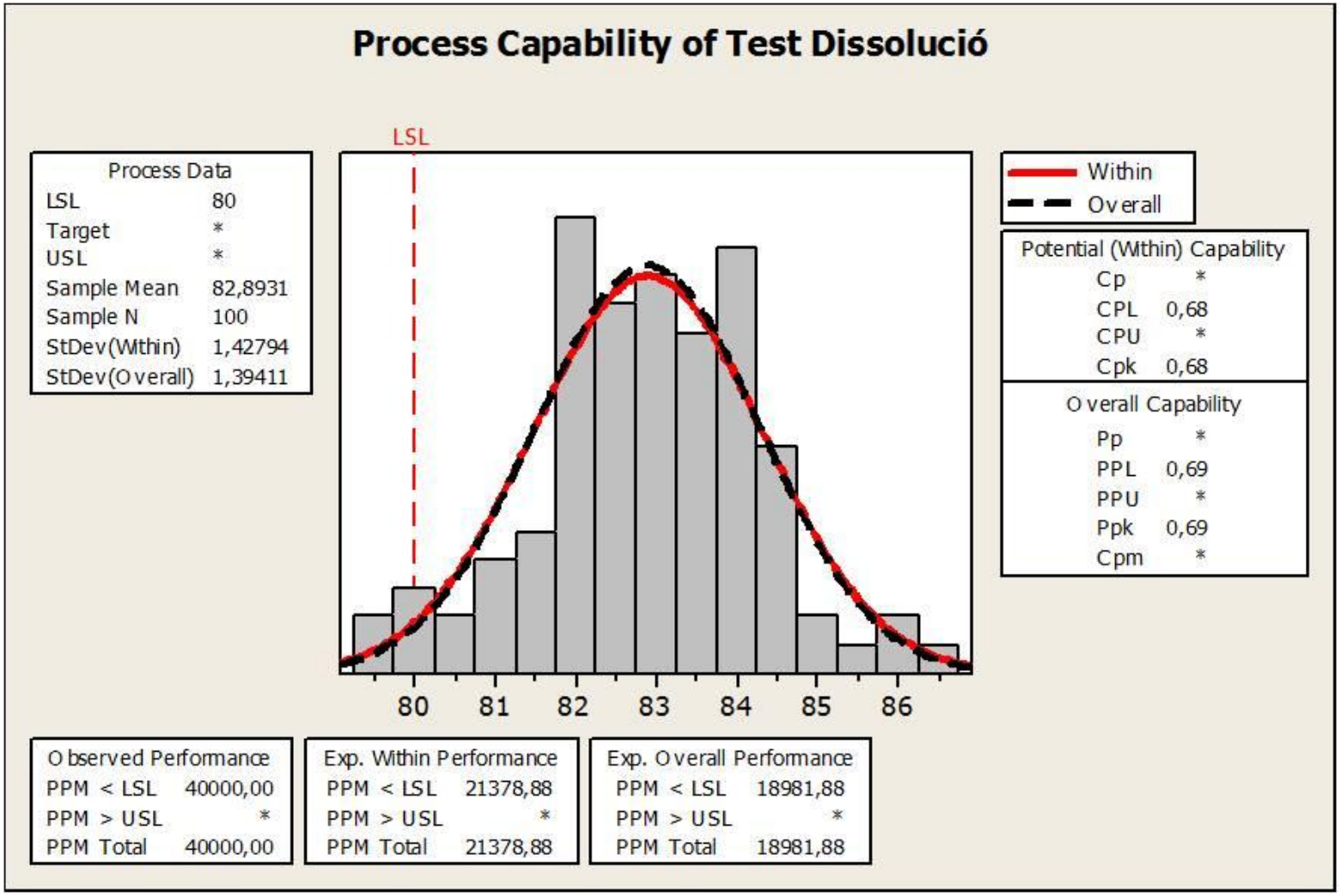


Process quality assessment



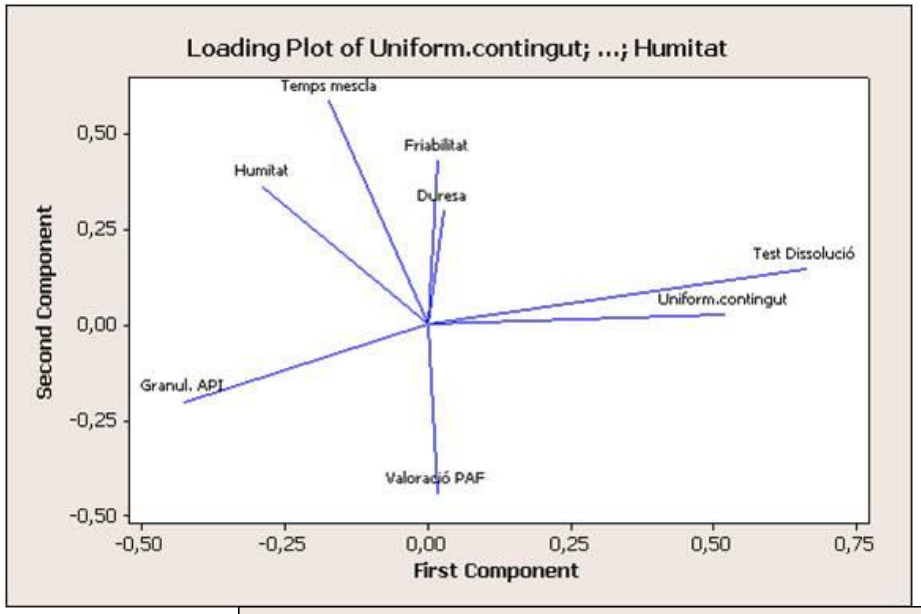
Risk of non conformity =9.7%

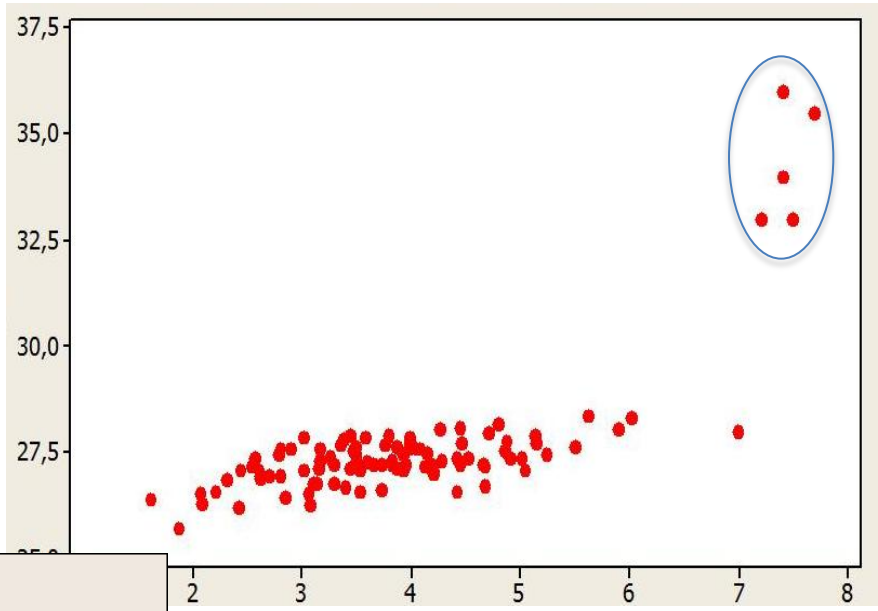
Process quality assessment

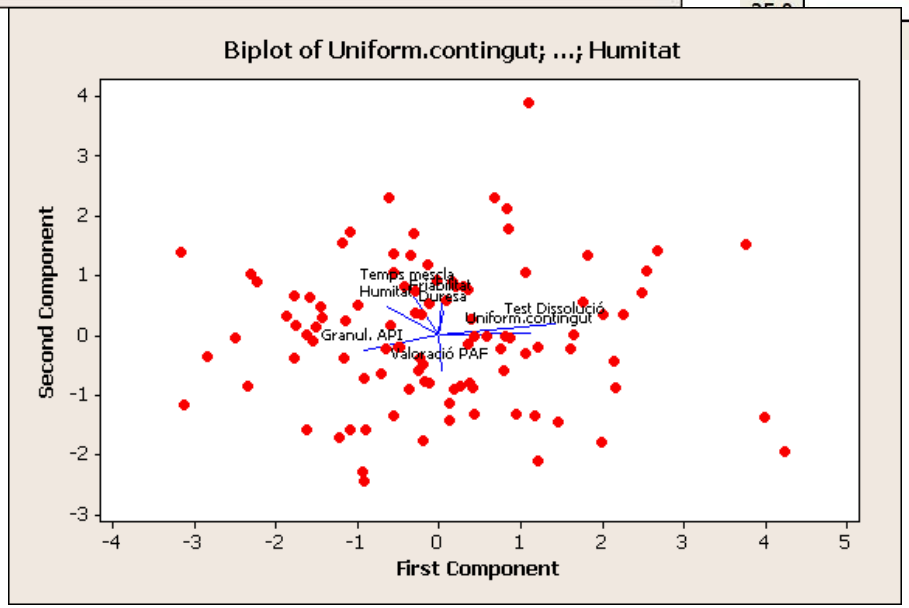


Risk of non conformity =1.9%

Process quality assessment (PCA)







ROI assessment

Anàlisis rendibilitat projecte QbD

Dades en Euros

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Estalvis										
Lots rebutjats		143.263	144.695	146.142	147.603	149.080	150.570	152.076	153.597	155.133
Lots amb anàlisis extra		4.889	5.036	5.187	5.342	5.503	5.668	5.838	6.013	6.193
Reducció temps de fabricació		61.207	61.207	61.207	61.207	61.207	61.207	61.207	61.207	61.207
Reducció temps d'anàlisis		5.081	5.234	5.391	5.553	5.719	5.891	6.067	6.250	6.437
Total Estalvis	**0**	**214.441**	**216.172**	**217.927**	**219.706**	**221.509**	**223.336**	**225.189**	**227.067**	**228.971**
Costs i despeses										
Inversions	240.000									
Modificació registre	15.000									
Cost proves DoE + Extra anàlisis	19.556									
Total despeses	**274.556**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

savings

investments

Anàlisis Cashflow

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Estalvis	0	214.441	216.172	217.927	219.706	221.509	223.336	225.189	227.067	228.971
Despeses	274.556	0	0	0	0	0	0	0	0	0
Cash-flow	**-274.556**	**214.441**	**216.172**	**217.927**	**219.706**	**221.509**	**223.336**	**225.189**	**227.067**	**228.971**
Cash-flow acumulat	**-274.556**	**-60.116**	**156.056**	**373.984**	**593.690**	**815.199**	**1.038.535**	**1.263.724**	**1.490.791**	**1.719.761**

VAN (tasa 10,5%) **877.733**

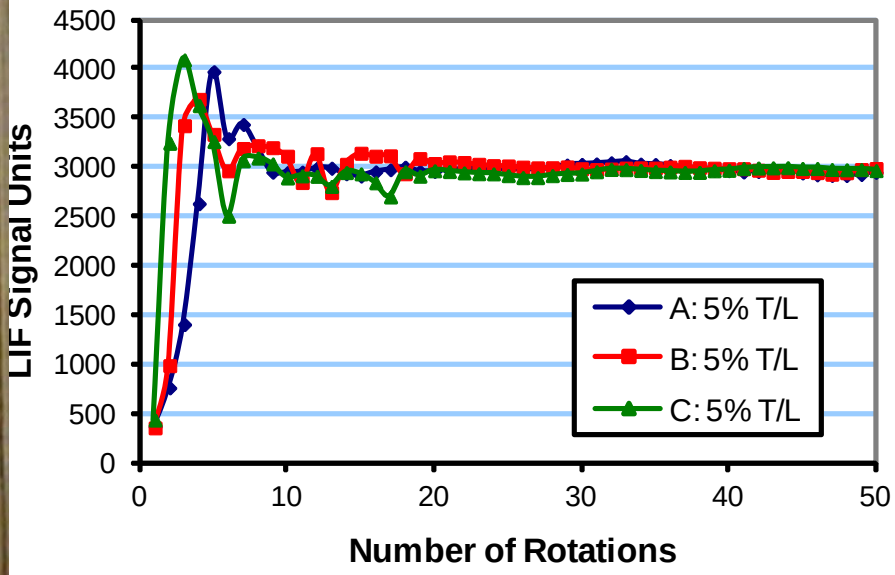
Payback (anys) **1,28**

Improvements…..



Introduce PAT:

Mixture End-point by NIR



Ishikawa to identify CMAs & CPPs

Figure 14 Ishikawa : content uniformity

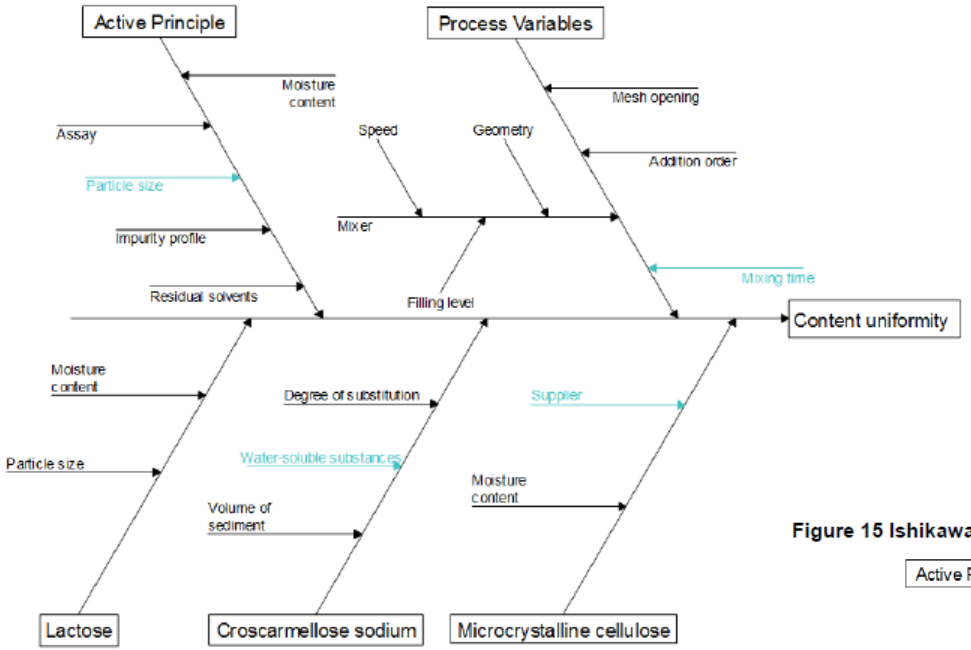
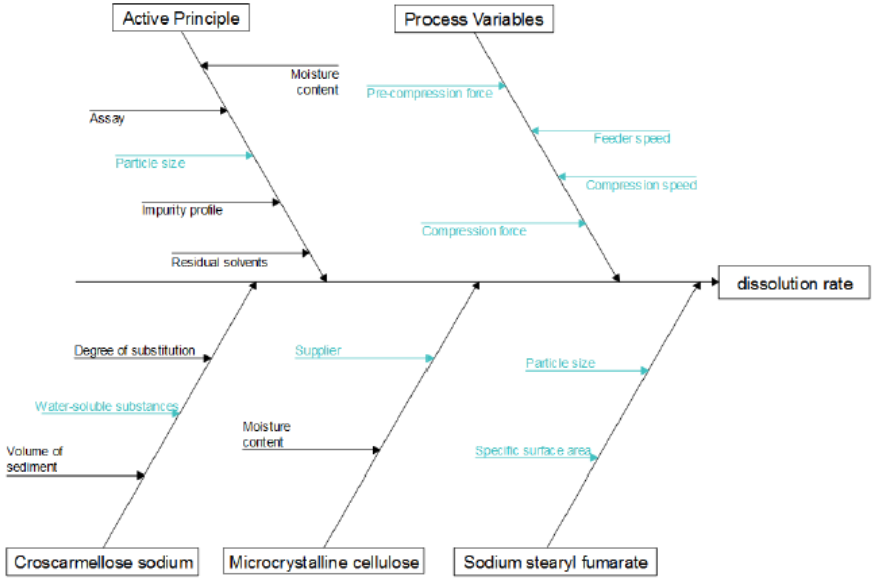


Figure 15 Ishikawa: dissolution rate



Risk analysis: CQA dissolution

Table 9 Tabletting step risk analysis: CQA is dissolution rate

CMA & CPP	Impact in the DR	Risk	Control strategy and DoE
Active ingredient purity	Medium	Can affect the average content even if it complies with the CU.	Control Raw material according to the specifications.
Active ingredient: particle size	High	Can affect the DR.	DoE studies 2 and 3. 3 levels Effect on percent dissolution.
Active ingredient: Impurities profile	Low	No effect on DR.	—
Active ingredient: Residual solvents	Low	No effect on DR.	—
Active ingredient: moisture	Low	API is not hygroscopic. No impact expected.	—

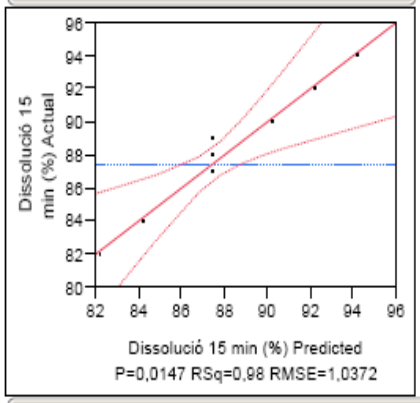
Risk analysis: CQA dissolution

Precompression force	High	Can affect the DR.	DoE study 3 3 levels Effect on hardness and percent dissolution.
Compression force	High	Can affect the DR.	DoE study 3 3 levels Effect on hardness and percent dissolution.
Charger speed	High	Can affect the DR.	DoE study 3 3 levels Effect on hardness and percent dissolution.
Compression speed	High	Can affect the DR.	DoE study 3 3 levels Effect on hardness and percent dissolution.

DoE to study impact of compression parameter in hardness & dissolution

Response Dissolució 15 min (%)

Actual by Predicted Plot

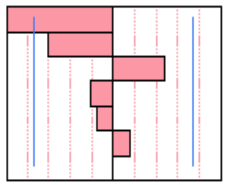


Analysis of Variance

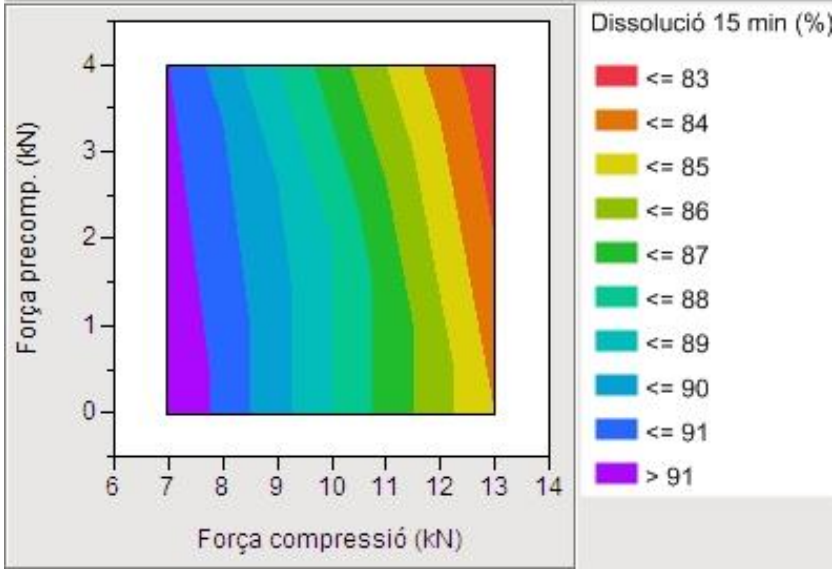
Source	DF	Sum of Squares	Mean Square	F Ratio
Model	7	159,50000	22,7857	21,1811
Error	3	3,22727	1,0758	Prob > F
C. Total	10	162,72727		0,0147*

Sorted Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Força compressió (kN)	-1,666667	0,386537	-4,31	0,0230*
Força precomp. (kN)	-1,5	0,579805	-2,59	0,0813
Velocitat (rpm)*Força precomp. (kN)	0,0375	0,018335	2,05	0,1334
Velocitat (rpm)	-0,133333	0,151688	-0,88	0,4441
Velocitat (rpm)*Velocitat FOM (rpm)	-0,005	0,007334	-0,68	0,5443
Velocitat (rpm)*Força compressió (kN)	0,0083333	0,012223	0,68	0,5443
Velocitat FOM (rpm)	0	0,231922	0,00	1,0000

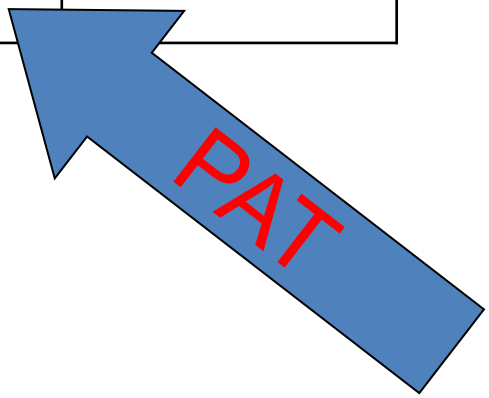


Contour Plot for Dissolució 15 min (%)



CONTROL STRATEGY PROPOSAL

Particle size API (d50)	SUPPLIER/ BRAND MCC:	Mixture time	Compression force
50-75 µ	X or Y (not Z)	End point by NIR	7-10 kN



Thank you

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