Aplicació sistemes qualitat pel disseny QbD als medicaments comercialitzats

Alicia Tébar
Azbil Telstar Projects

Tertúlies tecnològiques amb els amics del professor Ramon Salazar

6 Mars 2014.

- QbD in legacy products
  - *An ISPE (Spain) initiative: the case study.*
  - *¿What are we talking about?*
  - Regulatory framework (FDA & EMA)
- The Case Study
  - Contents of the document
  - The process & the quality problem
  - The process quality assessment
  - The ROI assessment
  - The improvements
  - The control strategy

XI Jornada Normes de Correcta Fabricació de medicaments.
Barcelona 12 /12/2013

Aplicació sistemes qualitat pel disseny QbD als medicaments comercialitzats

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ISPE

- Task force with 8 pharmaceutical companies and Spanish regulators to publish a document (2014) with **recommendations about QbD application to legacy products.**

European survey IQPC 2012

- Main reason to be skeptic about QbD
  - 2010 with 42%: business case and ROI not established
  - 2011 with 40%: QbD practices are difficult to integrate with current practices
  - 2012 with 59%: lack of qualified staff

A vicious circle

Development not oriented to manufacturability

Poor technology transfer and validation

Problems during commercial mfcture.

More resources to firefighting

Corrective actions = low efficiency

No feed-back production-development

A virtuous circle

Development oriented to manufacturability

Transfer /validation of a robust process.

Process under control = reproducible quality

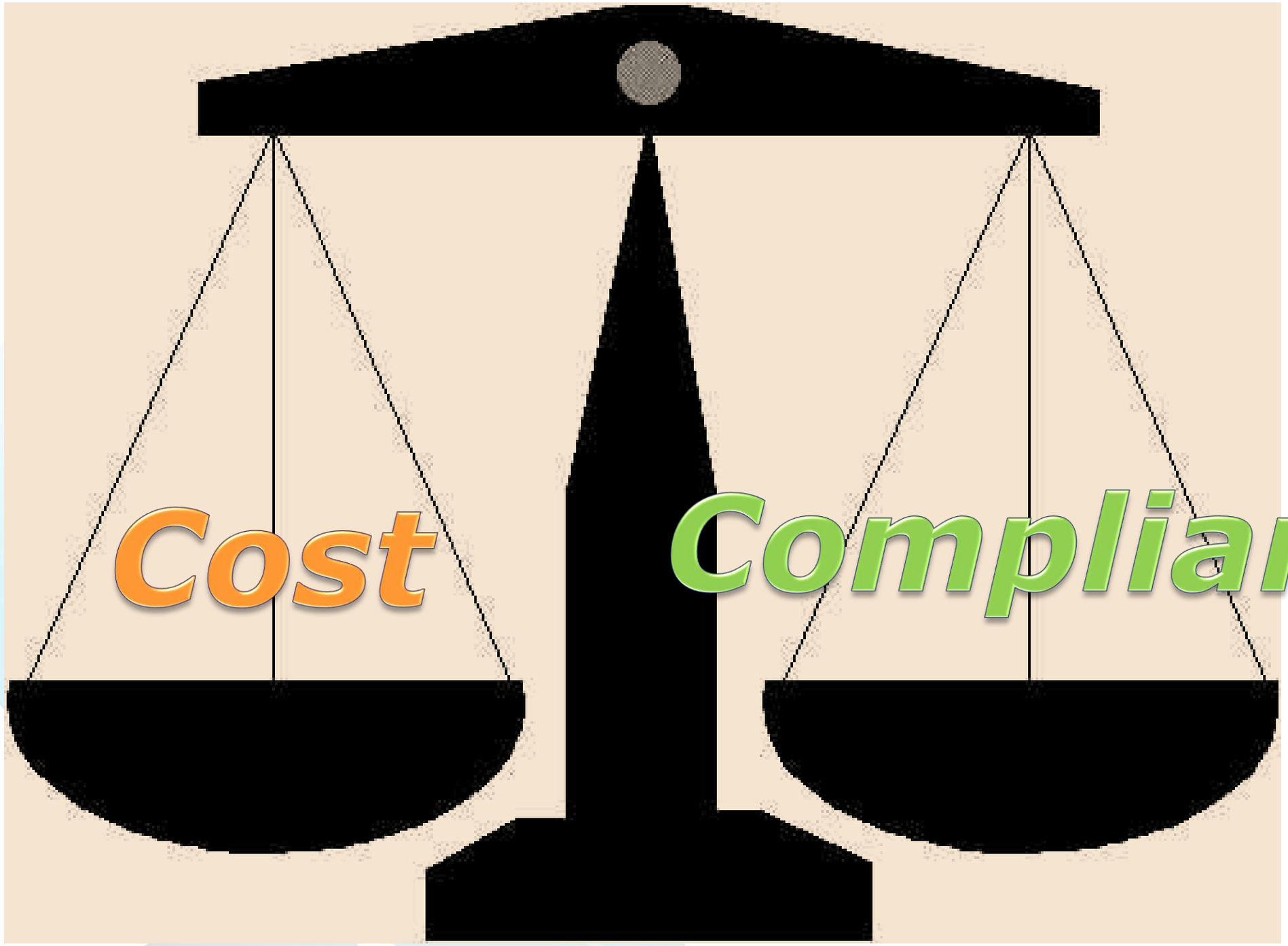
No firefighting= free quality/inspection resources

Preventive actions= high eficiency

Feed-back production-development

Desired state

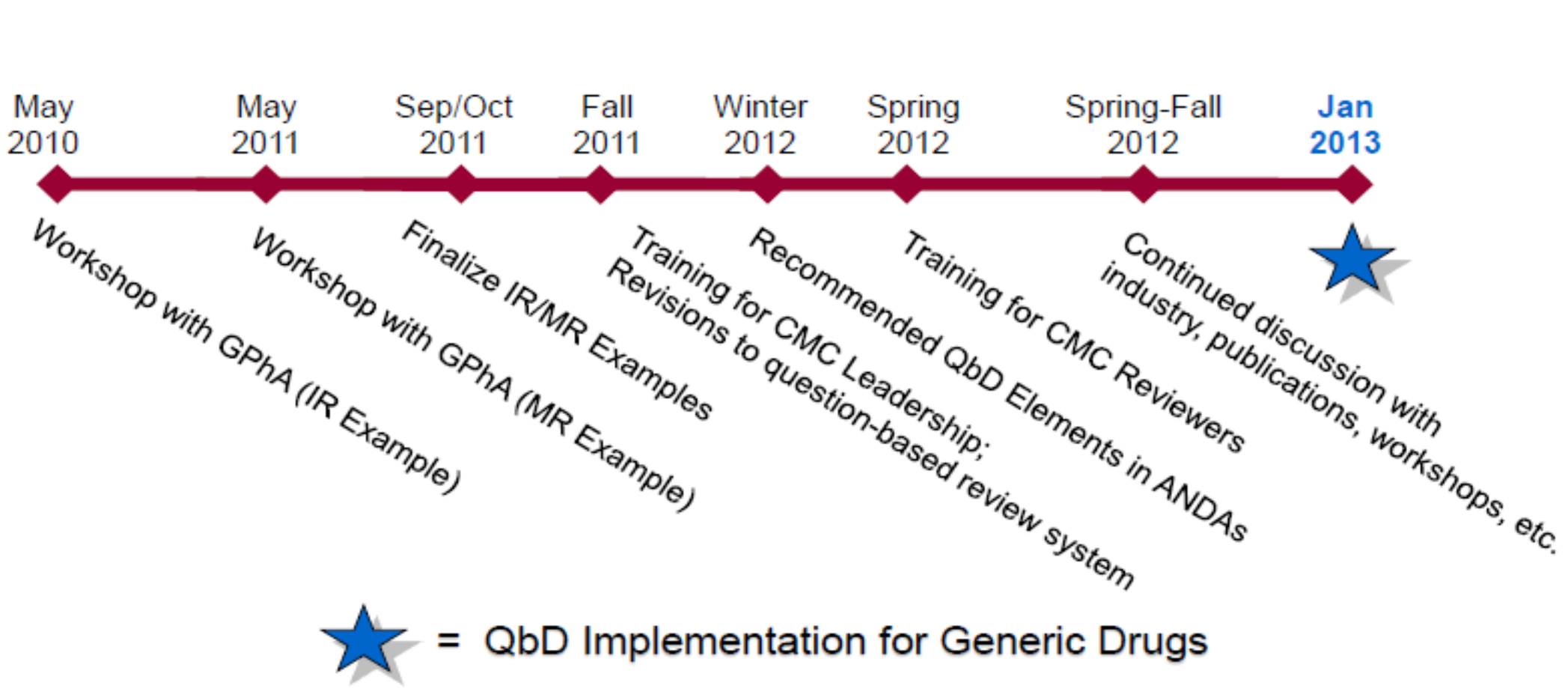
A virtuous circle



REGULATORY FRAMEWORK INDUSTRY TRENDS

Regulatory and normative milestones

"The US FDA is publishing immediate and modified release QbD examples to help generics companies prepare for full implementation in 2013"



Regulatory and normative milestones

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

29 March 2012
EMA/CHMP/QWP/811210/2009-Rev1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on Real Time Release Testing (formerly Guideline on Parametric Release)

Final

NEW CHAPTER 1 EU GMP's

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health Systems and Products
Medicinal Products - Quality, safety and efficacy

Brussels,
SANCO/AM/sl/ddg1.d.6(2012)860362

EudraLex

The Rules Governing Medicinal Products in the European Union

Volume 4

EU Guidelines for

Good Manufacturing Practice for

Medicinal Products for Human and Veterinary Use

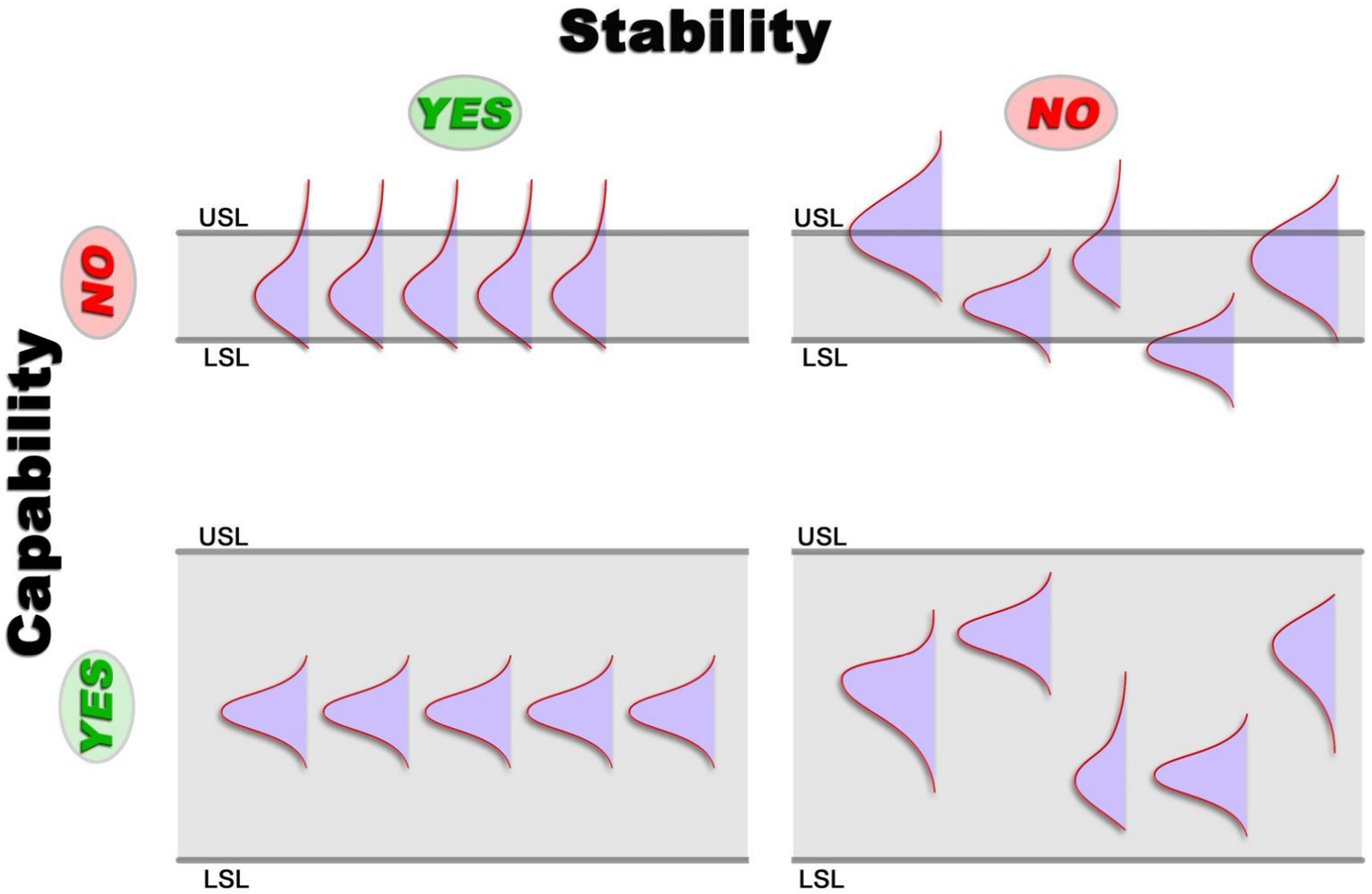
Chapter 1
Pharmaceutical Quality System

January 31th 2013

NEW CHAPTER 1 EU GMP's

- (viii) A state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality.
- (ix) The results of product and processes monitoring are taken into account in batch release, in the investigation of deviations, and, with a view to taking preventive action to avoid potential deviations occurring in the future.

Process performance requirements



indicators

Quarter and Year	Ppk	Pp	Cpk	Cp	Stability Index	Short-Term Sigmas From Target	Avg	Short-Term Sigma	Long-Term Sigma	LSL	Target	USL
1Q 2003	1.52	1.62	2.90	3.09	1.91	0.56	70.3	0.54	1.03	65	70	75
2Q 2003	1.63	1.70	2.71	2.82	1.66	0.34	70.2	0.59	0.98	65	70	75
3Q 2003	1.45	1.52	2.96	3.09	2.04	0.37	69.8	0.54	1.10	65	70	75
4Q 2003	1.65	1.68	3.33	3.40	2.02	0.20	69.9	0.49	0.99	65	70	75
1Q 2004	1.75	1.75	3.21	3.21	1.83	0.00	70.0	0.52	0.95	65	70	75
2Q 2004	1.61	1.75	2.69	2.92	1.67	0.70	69.6	0.57	0.95	65	70	75
3Q 2004	1.49	1.59	2.85	3.03	1.91	0.55	70.3	0.55	1.05	65	70	75

Lifecycle approaches to process validation

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 29 March 2012
2 EMA/CHMP/CVMP/QWP/70278/2012-Rev1
3 Committee for Medicinal Products for Human Use (CHMP)
4 Committee for Medicinal Products for Veterinary Use (CVMP)

5 Guideline on Process Validation
6 Draft

Guidance for Industry

Process Validation: General Principles and Practices

Additional copies are available from:

Office of Communications
Division of Drug Information, WO51, Room 2201
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

New Annex 15 EU GMPs: Qualification & Validation

Continuous process verification

4.21 For products developed by a quality by design approach, where it has been scientifically established that routine process control provides a high degree of assurance of product quality, then continuous process verification can be used as an alternative to traditional process validation.

4.22 The process verification system should be defined and there should be a science based control strategy for the required attributes for incoming materials, critical quality attributes and critical process parameters to confirm product realisation. This should also include regular evaluation of the control strategy. Process Analytical Technology and multivariate statistical process control may be used as tools. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product.

4.23 The general principles in 4.1 – 4.15 above still apply.

4.24 A hybrid approach using the traditional approach and continuous process verification for different production steps can also be used. Where there is a substantial amount of product and process knowledge and understanding which has been gained from manufacturing experience and historical batch data, continuous verification may also be used for any validation activities after changes or during ongoing process verification even though the product was initially validated using a traditional approach.

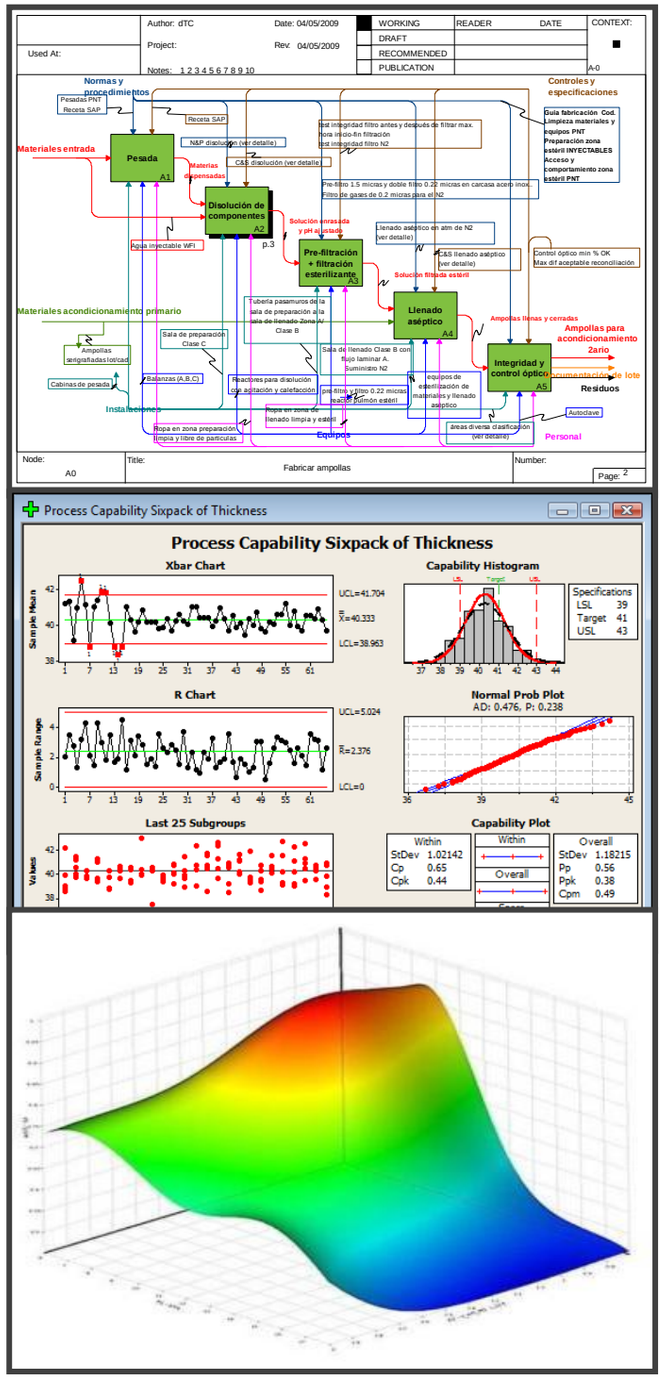
Ongoing Process Verification during Lifecycle

4.25 Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated.

Expected adoption: october 2014

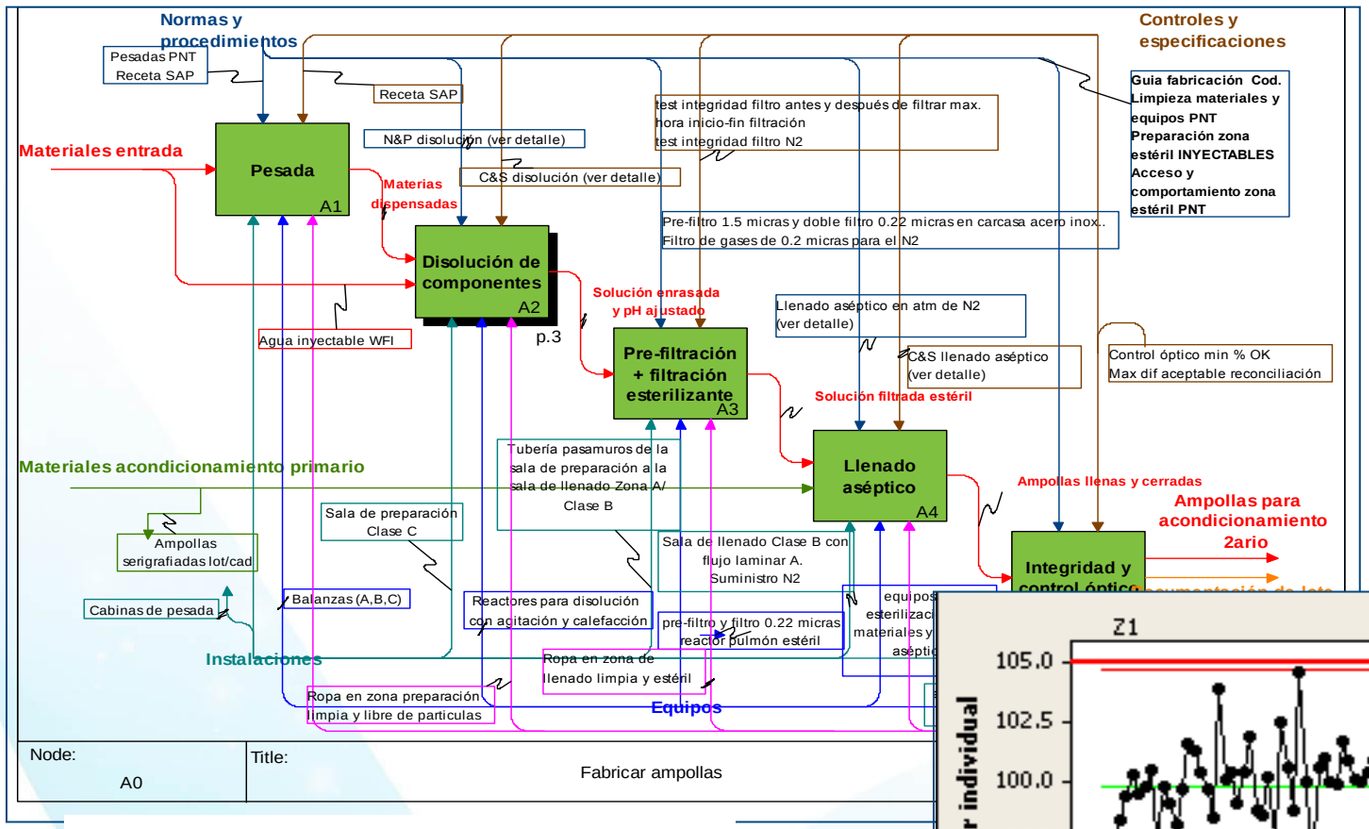
QbD/PAT Projects

- **New & legacy/drug substance & product**
  - **Application of ICH Q8 & Q11:**
    - Development of new products
    - Reengineering of legacy products
  - **Knowledge management:**
    - Process risk analysis: project management of multidisciplinary teams.
    - IT, data collection and data mining
  - **Quality Systems. ICH Q10.**
    - Process mapping. Quality Manual.
    - Process monitoring systems
    - New approaches to validation

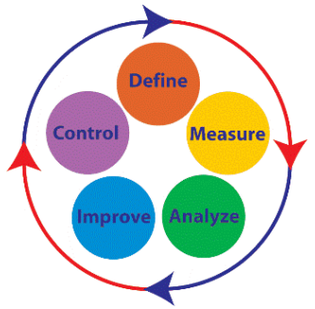


Improvement Projects

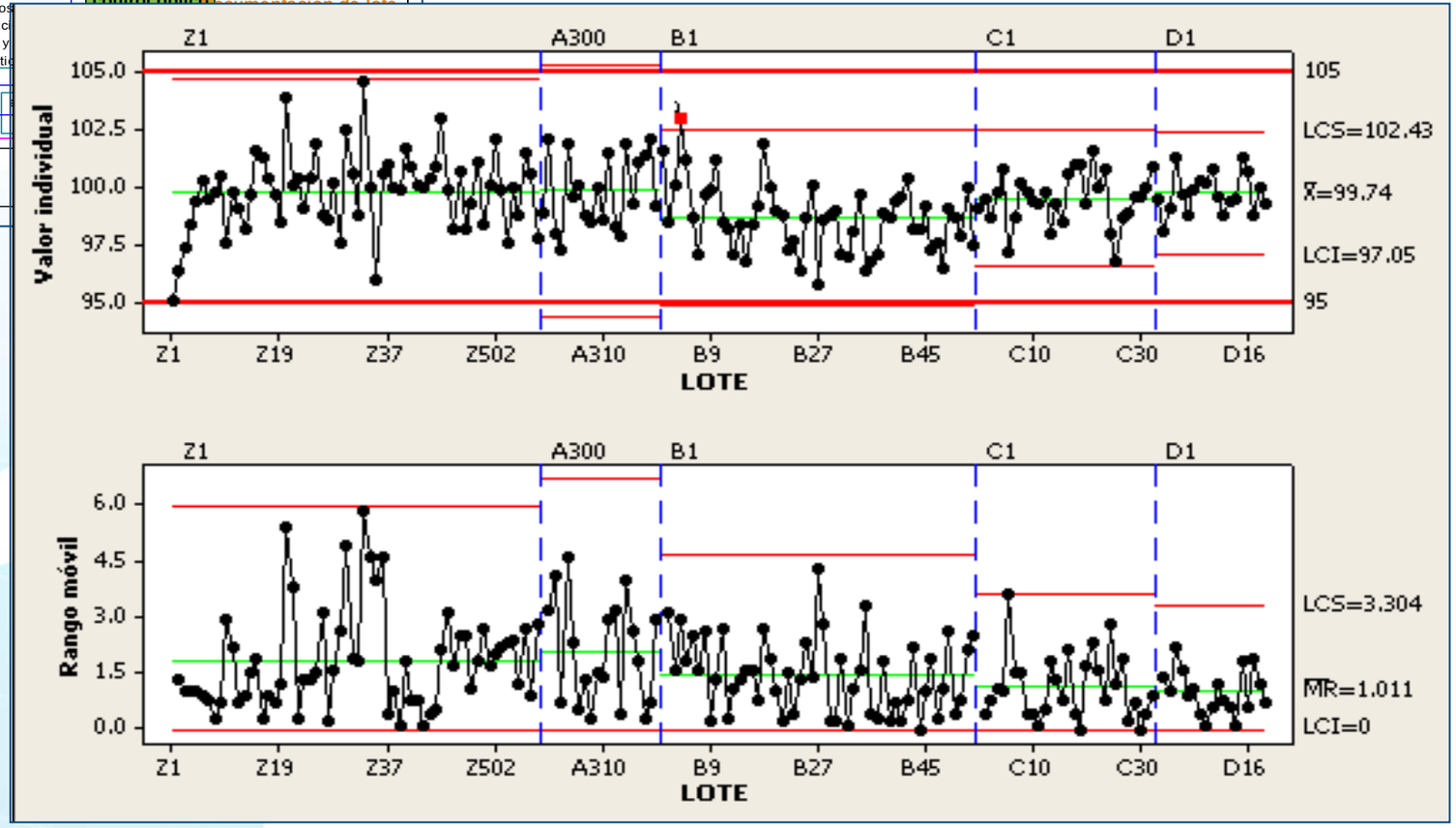
- Process improvement: process mapping & risk analysis



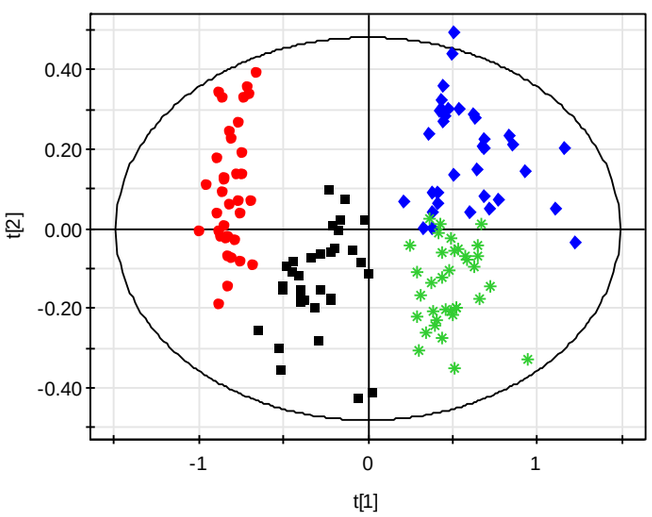
Lean- 6 Sigma



- Variability reduction



NIRChipT.M1 (PCA-X), PCA for overview
t[Comp. 1]/t[Comp. 2]



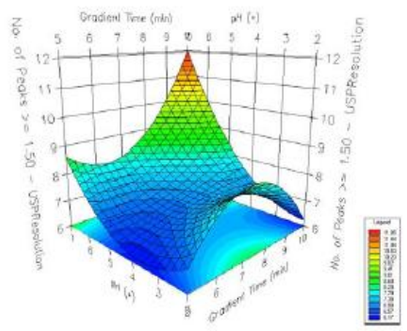
The Case Study

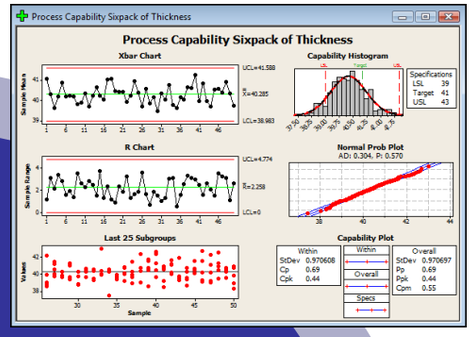
Connecting a World of Pharmaceutical Knowledge

Spain Affiliate

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

Industry & regulators working together





PK

PP&C

ROI

€

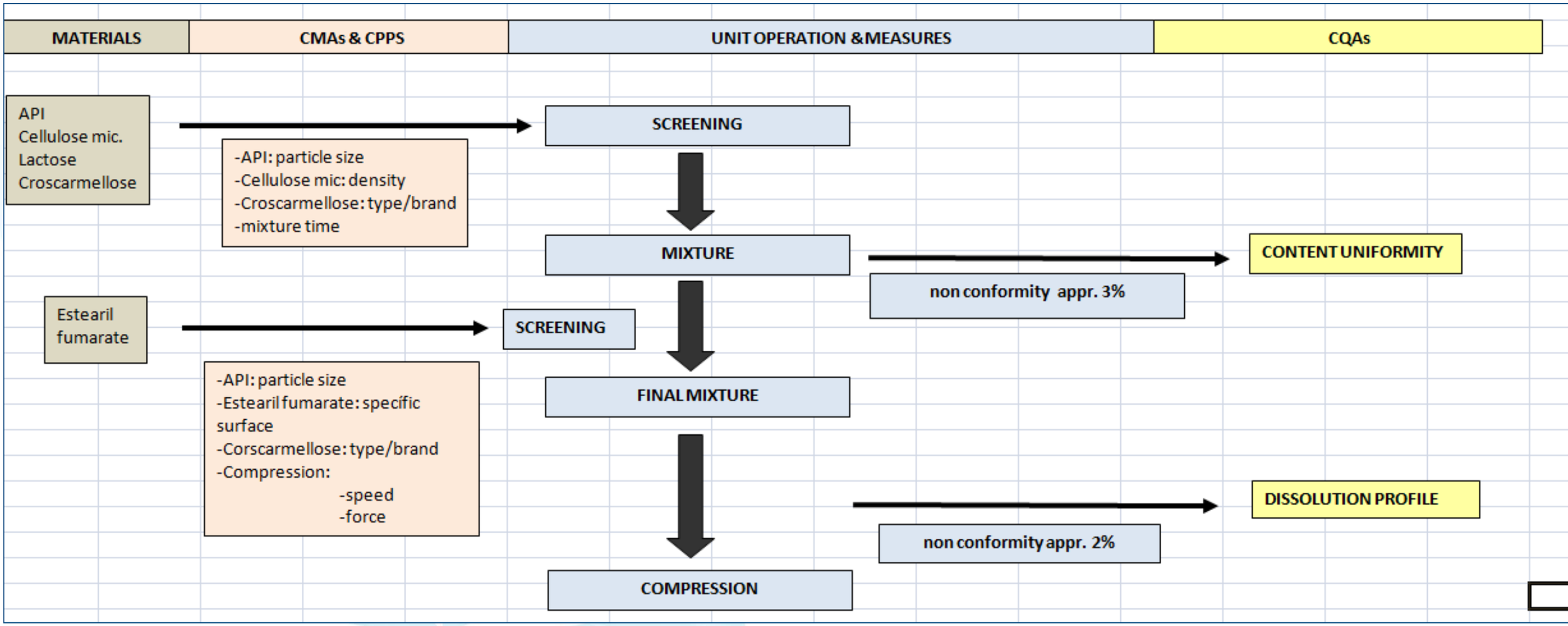
Recomanacions per a l'aplicació de sistemes de gestió de la qualitat pel disseny (QbD) en la fabricació industrial de medicaments¶
(versió final elaborada pel grup de treball – (28 d'octubre de 2013)¶

Index¶
¶

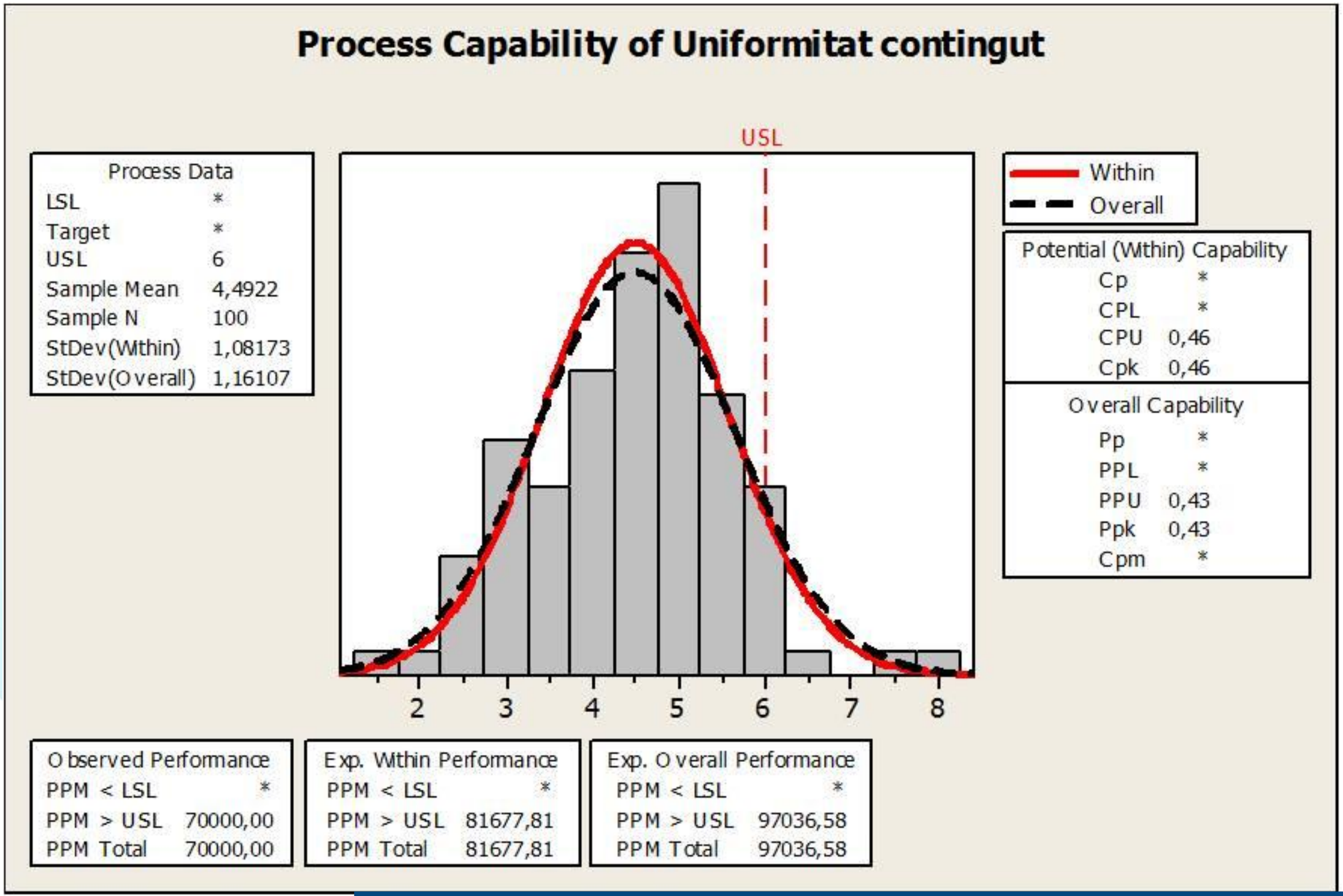
Document contents

1. Background, aim and scope.
2. Evaluation of the “state of control” of manufacturing processes.
3. Evaluation of design & knowledge deficiencies of manufacturing processes and improvement proposal.
4. Calculating the ROI of a QbD project.
5. Case Study.

The process & the quality problem

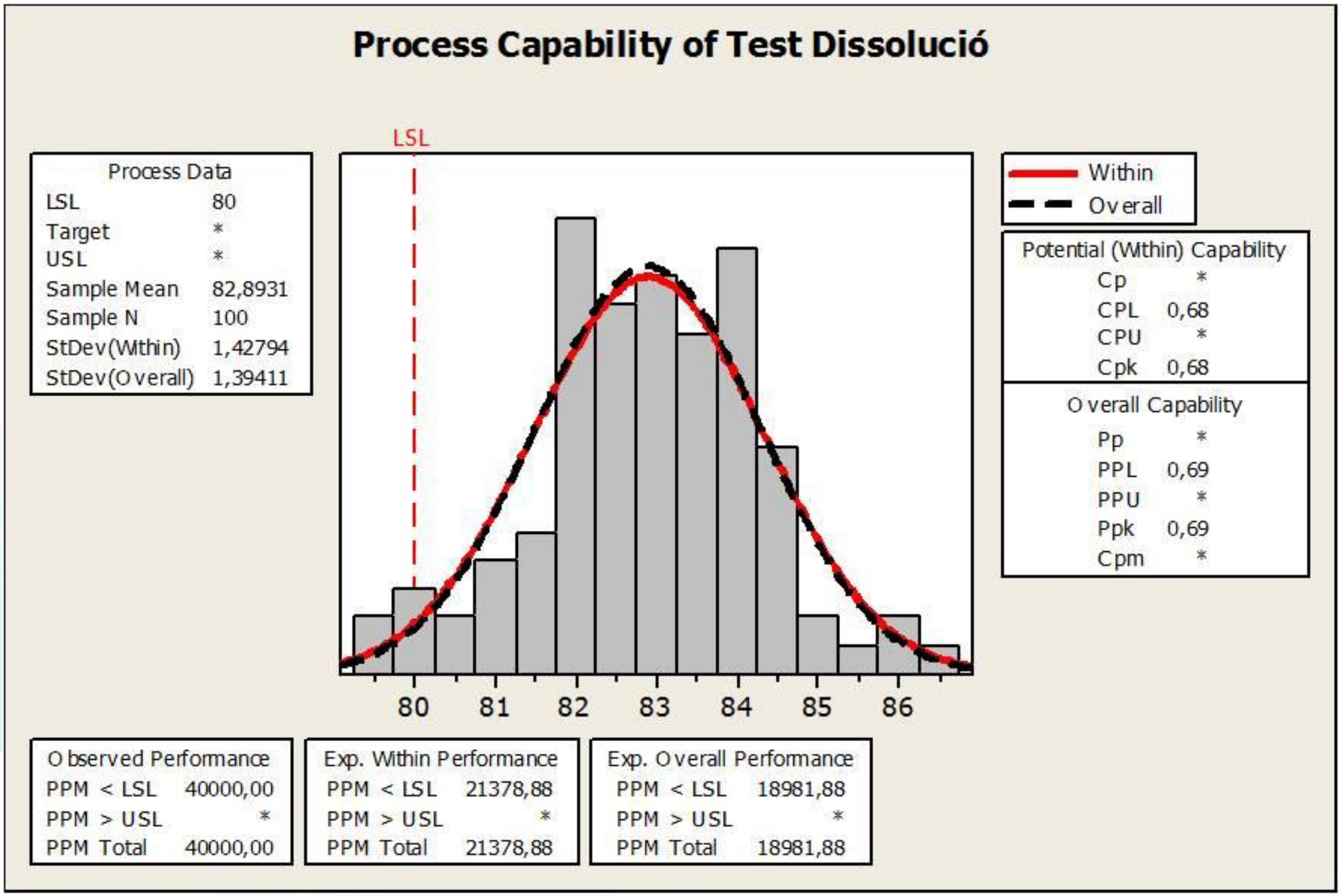


Process quality assessment



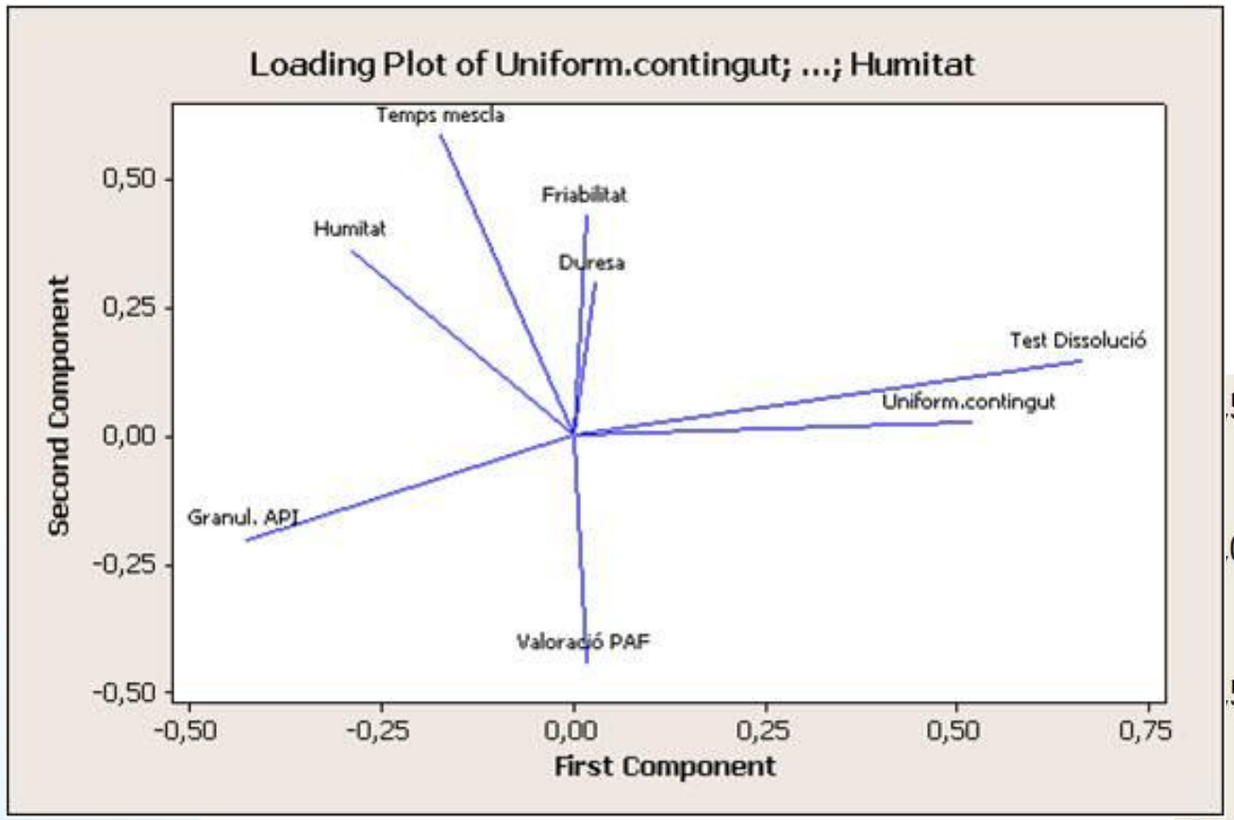
Risk of non conformity =9.7%

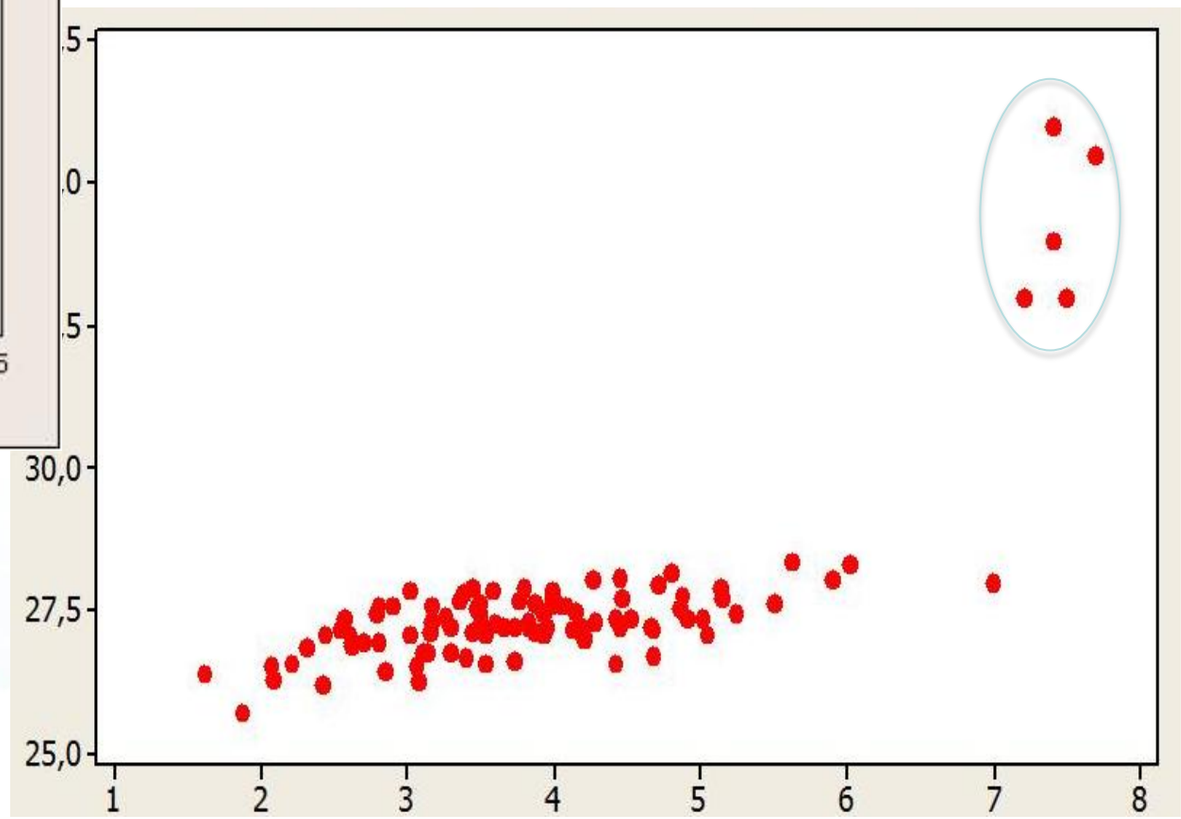
Process quality assessment

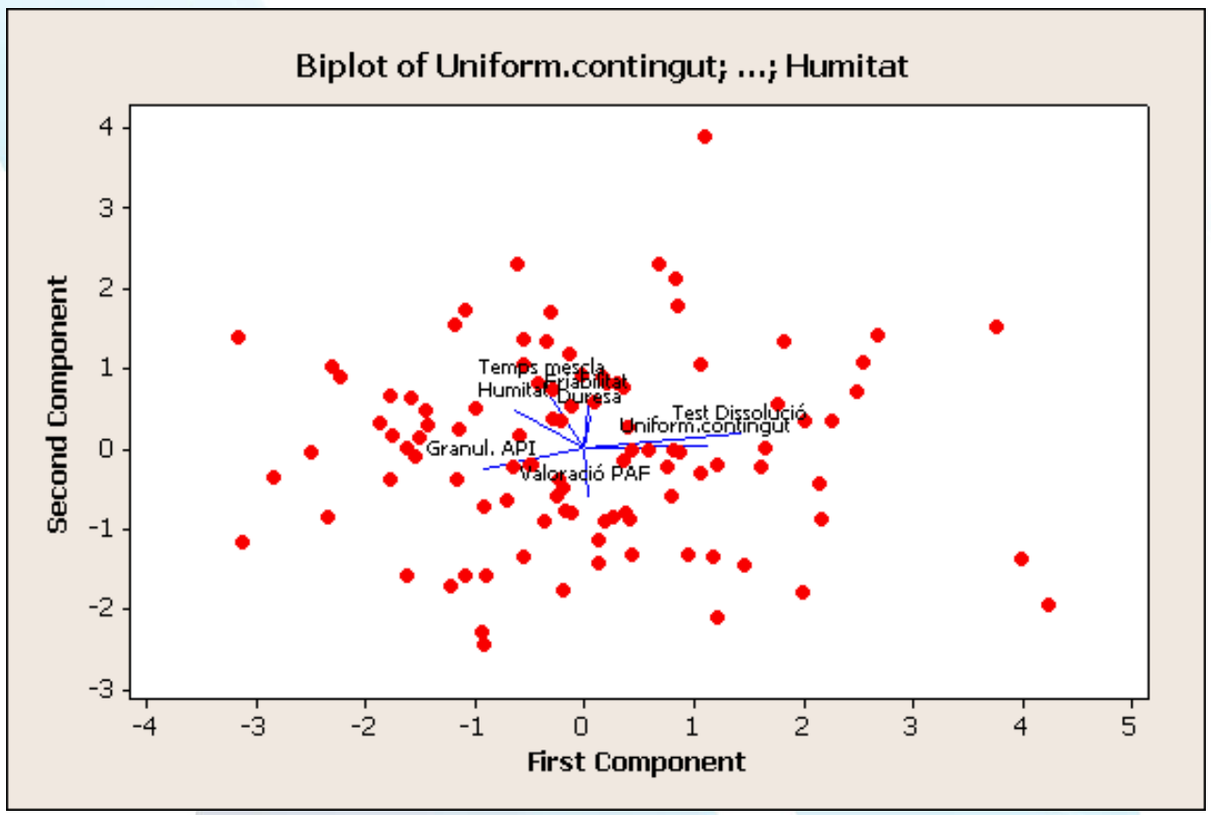


Risk of non conformity =1.9%

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
savings										
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**
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**

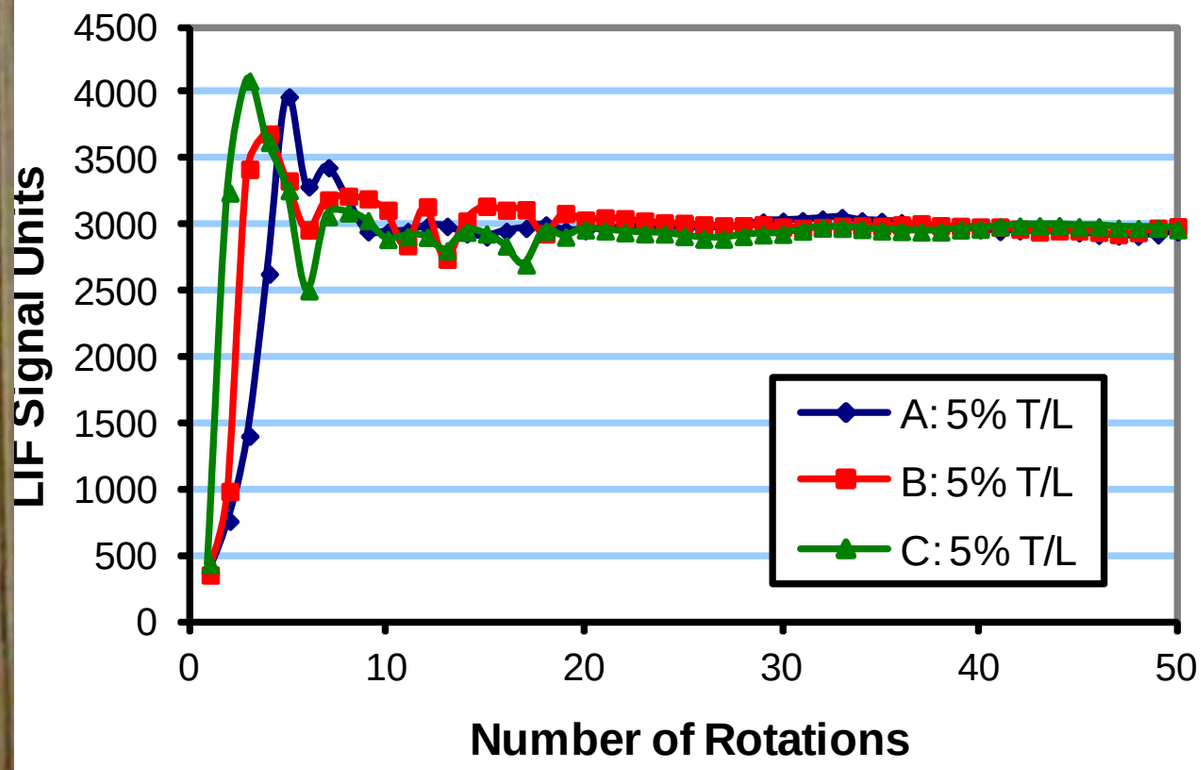
VAN (tasa 10,5%) **877.733**

Payback (anys) **1,28**

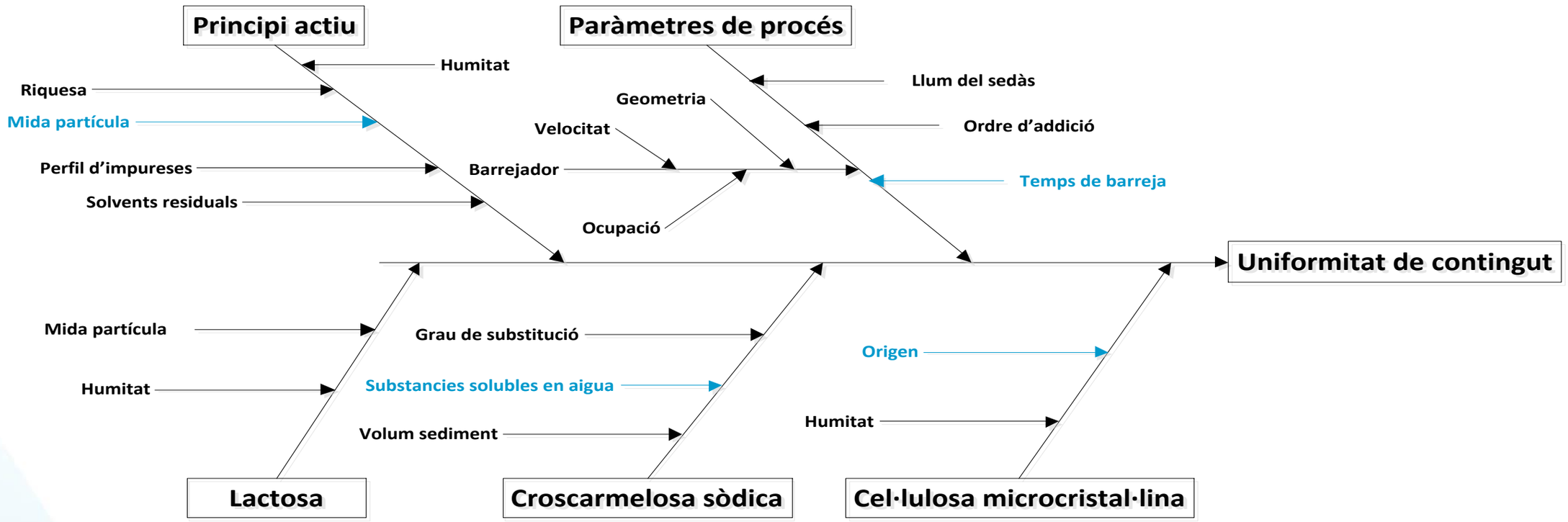
Improvements.....

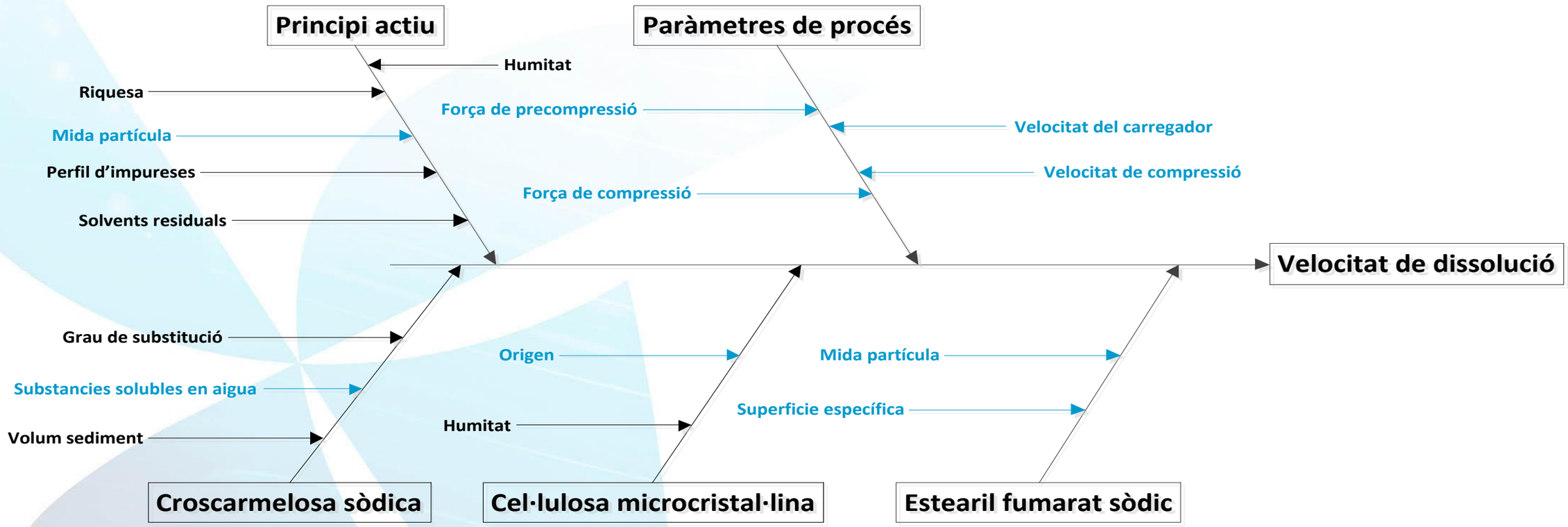
Introduce PAT:

Mixture End-point by NIR



Ishikawa to identify CMAs & CPPs





Risk analysis: CQA dissolution

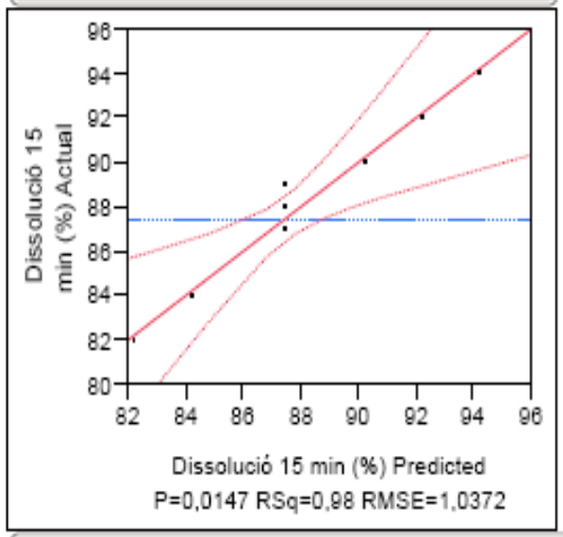
CMAs	IMPACTE	Racional DoE
API: Riquesa	MIG	Mantenir cte. Specs MMPP
API: Mida Part.	ALT	Estudiar en 2 DoEs 3 nivells
API: Perfil Imp.	BAIX	NA
API: Con't….		
Esteraril Fum. Na: Mida Part.	ALT	Estudiar en 2 DoEs 3 nivells
Resta excip i CMA de cadascún:….		

CPP	IMPACTE	Racional DoE
Força Pre-compressió	ALT	Estudiar en 1 DoE. 3 nivells
Força Compressió	ALT	Estudiar en 1 DoE. 3 nivells
Velocitat del carregador (FOM)	ALT	Estudiar en 1 DoE. 3 nivells
Con't….		

- *DoE to study impact of compression parameter in hardness & dissolution*

Response Dissolució 15 min (%)

Actual by Predicted Plot



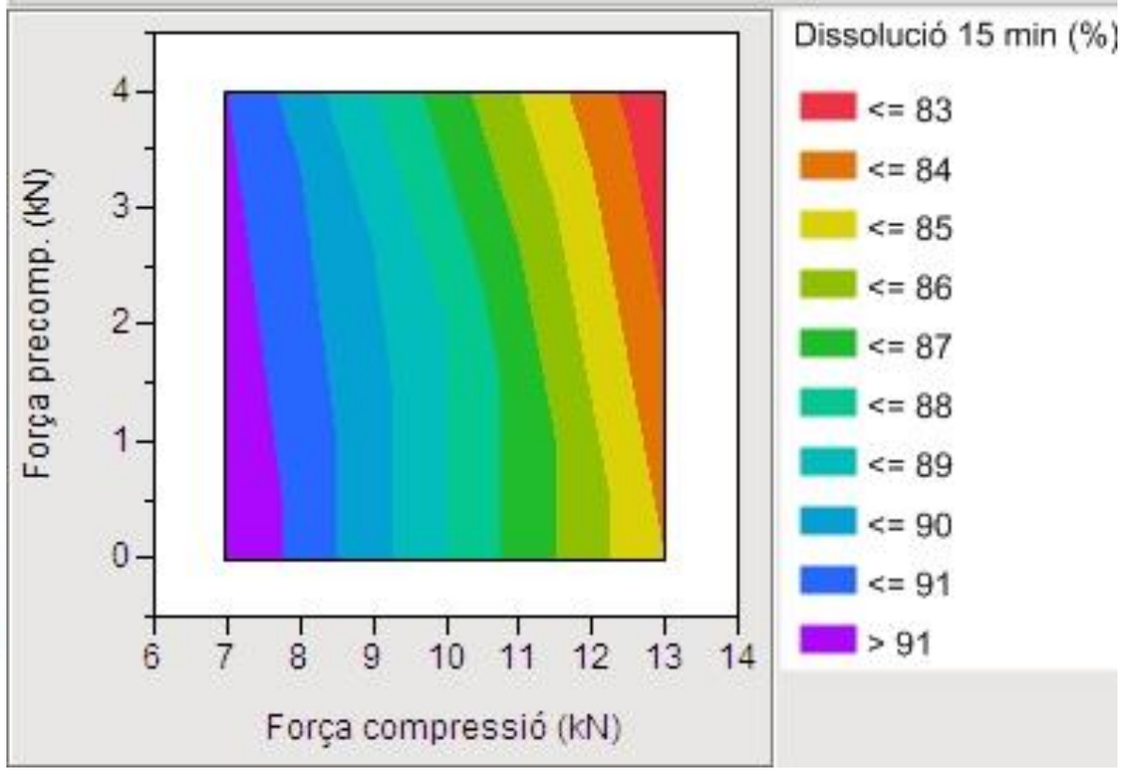
Analysis of Variance

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

PAT

MOLTES GRÀCIES

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www.qbd-dtc.com