PHARMAprocess

Innovation Forum in Pharmaceutical Process

QbD at minimum or full application

How to apply QbD in a SMART way?

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Track 1: REGULATORY & DEVELOPMENT

Management strategy to reduce time to market

After more than a decade since the FDA initiative, the implementation of QbD in pharmaceutical development has become widespread in the drug companies. Especially for those oriented to the American market where the FDA establishes minimum QbD content to present, in order to demonstrate the scientific basis on which products and processes are designed to achieve consistent quality and stable manufacturing since the first industrial batch.

To some extent, the idea that still persists is that implementing QbD is complex and / or expensive despite the obvious advantages.

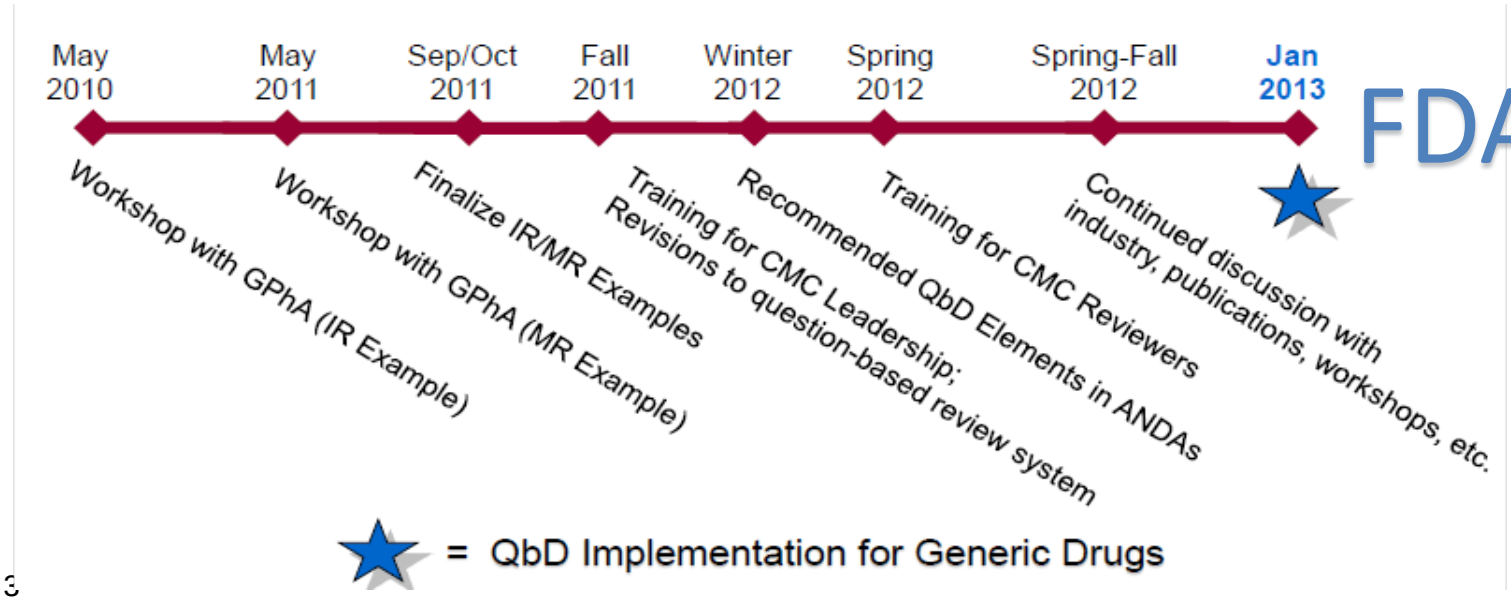
SMART QbD is a methodology that adapts to the timing and project constraints but providing appropriate tools to optimize the acquisition of the key knowledge about the product/process with the available resources.

QbD Regulatory

Guidance for Industry
PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

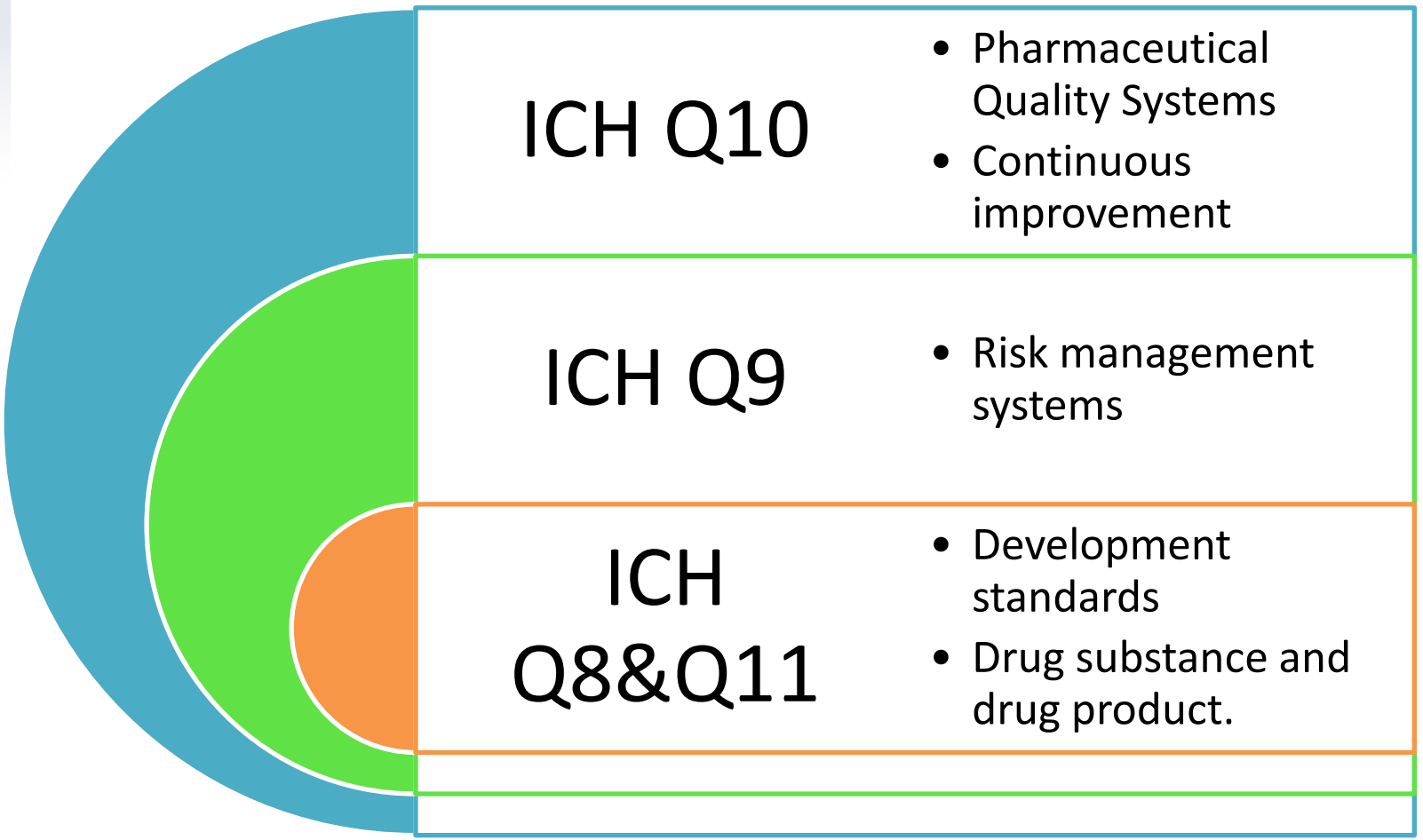
FDA 2004

"quality cannot be tested into products; it should be built-in or should be by design"

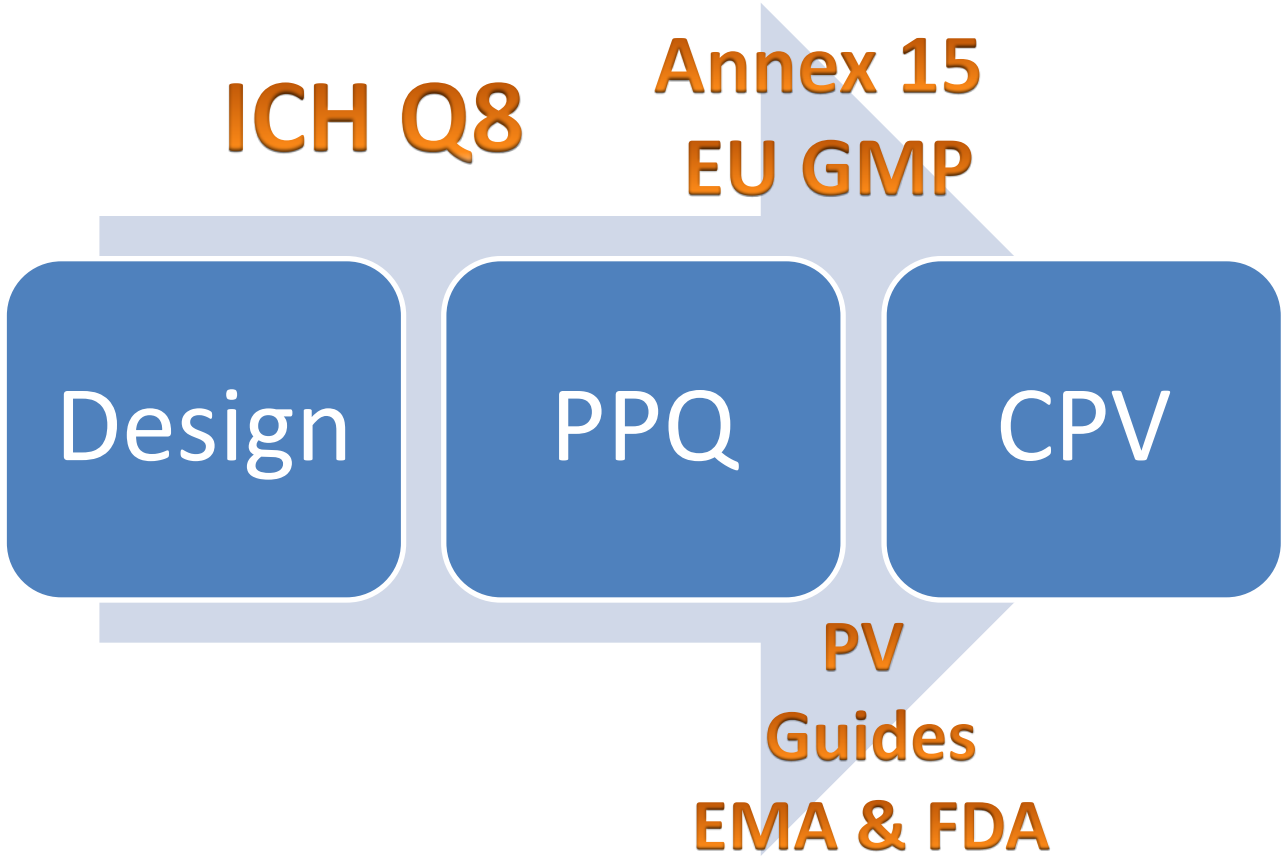


FDA 2013

QbD .....GMP


ICH Q10
• Pharmaceutical Quality Systems
• Continuous improvement
ICH Q9
• Risk management systems
ICH Q8&Q11
• Development standards
• Drug substance and drug product.

QbD .....GMP



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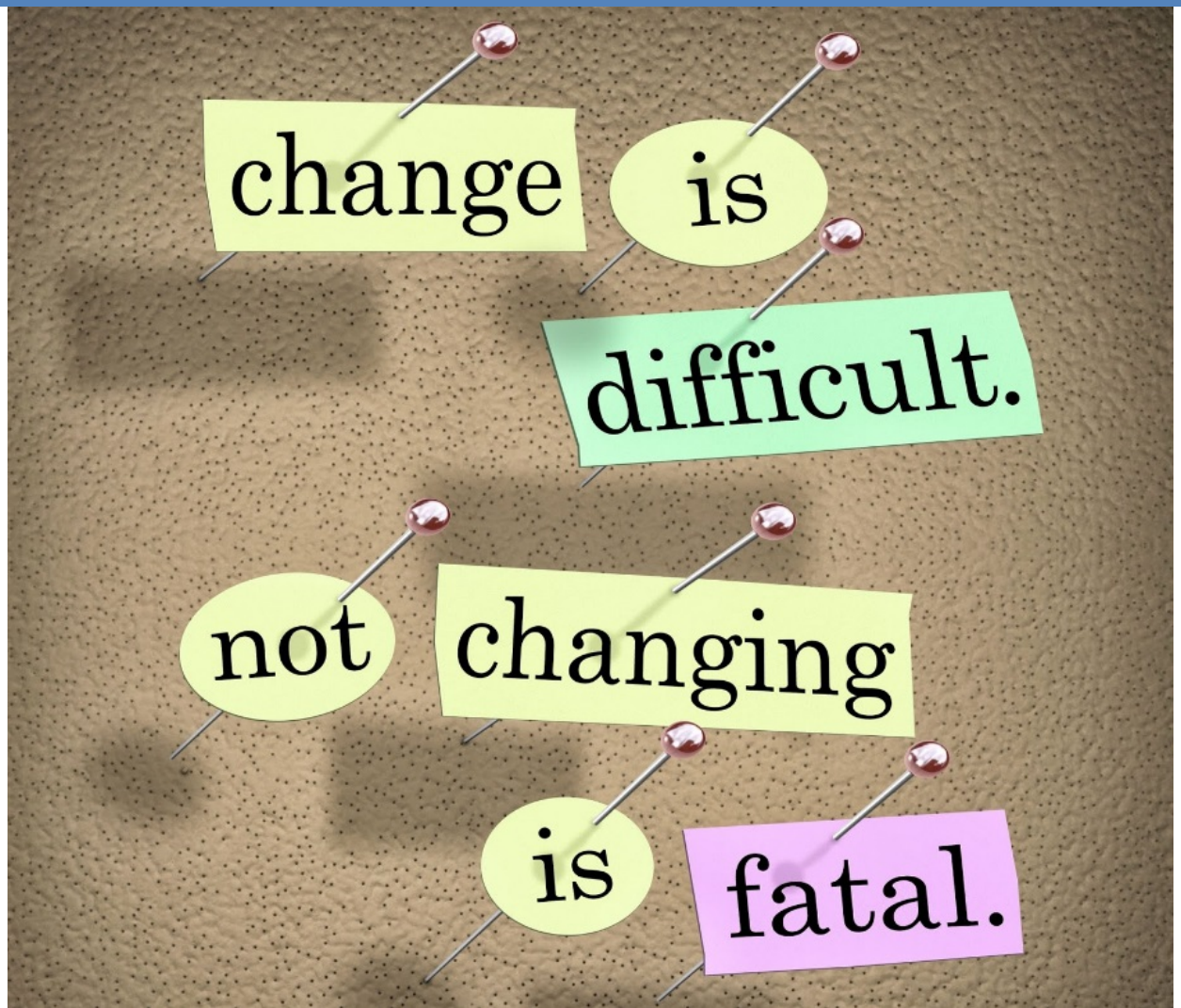
Minimum or full QbD? Nowadays is it an option no-QbD?

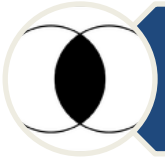


A SMART approach to QbD


Specific

Measureable


Attainable


Relevant


Time Based

SMART is an acronym to describe characteristics of the well fitted objectives in a project.

SMART really fits well also in the methodology definition.

It is common sense to be smart in applying QbD.

Being SMART in Quality by Design: SMART QbD

Focused on your project needs.

Adapts to the project goals and constraints in different situations:

- New drug product or substance full development.
- Generic pharmaceutical development.
- Redesign and /or optimisation of unit operations or full industrial process (legacy products).

Being SMART in Quality by Design: SMART QbD

Focused on data.

Applies statistics to your data to increase product and process knowledge and to take the right decisions .

- It is not necessary to start from scratch. All previous knowledge/testing is valuable and can be treated with the most suited statistical tool to reveal key information in order to reduce and orient future trials and DoE.

Being SMART in Quality by Design: SMART QbD

Focused on attaining project goals.

Include project management tool DMAIC (Six Sigma) specially adapted to QbD projects. A Project Charter defines objectives, resources and constraints. If necessary a ROI statement can be prepared to assess the project financially.

- Business Case definition.
- Define project milestones.

Being SMART in Quality by Design: SMART QbD

Focused on what is relevant.

Include Risk Analysis tools adapted to the different stages during development: pre-DoE, post-DoE, pre-validation etc.

- RA tool uses previous knowledge to define “platform” unit operation templates that are re-usable. This is a key feature to save time for future similar projects.
- RA tool is designed to be collaborative to ease knowledge sharing and to reduce the need for endless RA meetings.

Being SMART in Quality by Design: SMART QbD

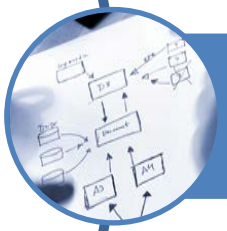
Focused on getting results on-time.

Taking into account time constraints, that sometimes is time to market goals, in different ways:

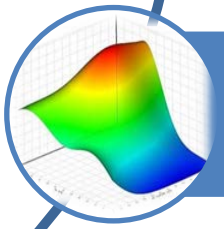
- Taking advantage of previous knowledge/trials.
- Defining what is missing (and necessary) for project goals.
- Using Design of Experiments advanced features to minimise the number of trials: D-optimal designs, definitive screening designs etc.

Tools for SMART QbD

Project management



Risk analysis



Design of experiments

Project management

Project Charter:

- Goals
- Resources
- Responsibilities
- Timings
- ROI (if improvement project)

PROYECTO SIX SIGMA	Producto XXXXXXXX
Objetivos del proyecto	
XXXXXXXXXXX	
Importancia del proyecto/ Riesgos	**Ámbito/límites del proyecto**
Impacto en clientes externos: • Pacientes: Impacto en la eficacia • Autoridad reguladora: Impacto en clientes internos: • Cadena de producción	Producto • XXXXXXX Proceso • YYYYYYYY Fases del proceso • XXXXXXXX
Objetivos de mejora del proyecto	
MÉTRICAS Ppk para el contenido de XXXXXXXX mínimo 1, deseable 1.3 Nivel σ para el contenido de XXXXXXX: mínimo 3σ, deseable 4σ Orientativo: Índice de estabilidad (contenido XXXXXXXX) < 1.67	

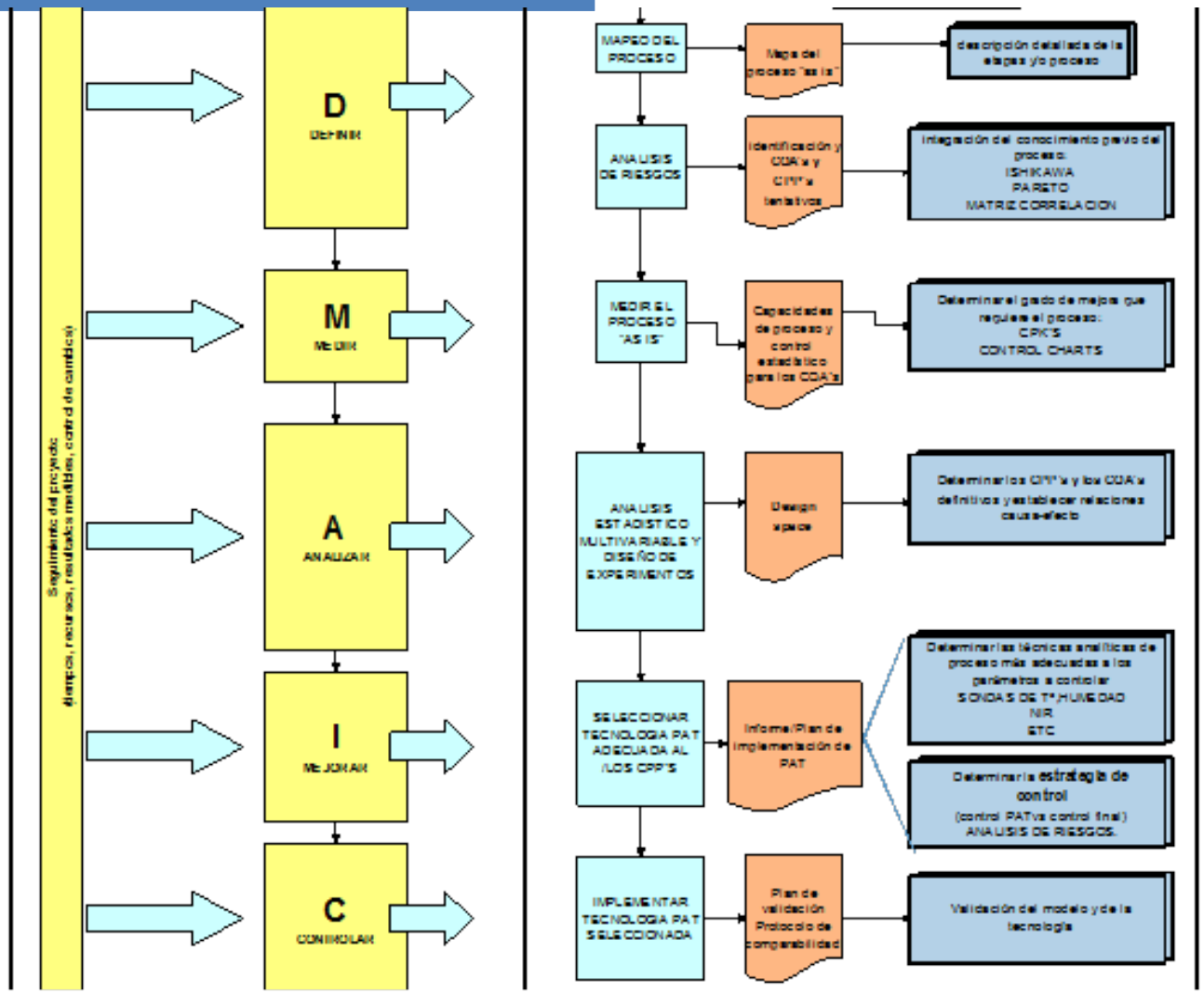
Estimación del ahorro (anual)			
Concepto	**Coste actual**	**Coste previsto**	**Ahorro**
		Ahorro total	

Inversiones necesarias / coste del proyecto		**Retorno de la inversión. ROI**
Concepto	**Coste**	**ROI=coste total/ahorro total anual=**
Coste total proyecto		

Miembros del equipo	Coordinador Black Belt:
Champion:	Miembro:

Calendario de tareas				
Fase	**Actividad**	**Inicio**	**Final**	**Revisión**
Define				
Measure				
Analyse				

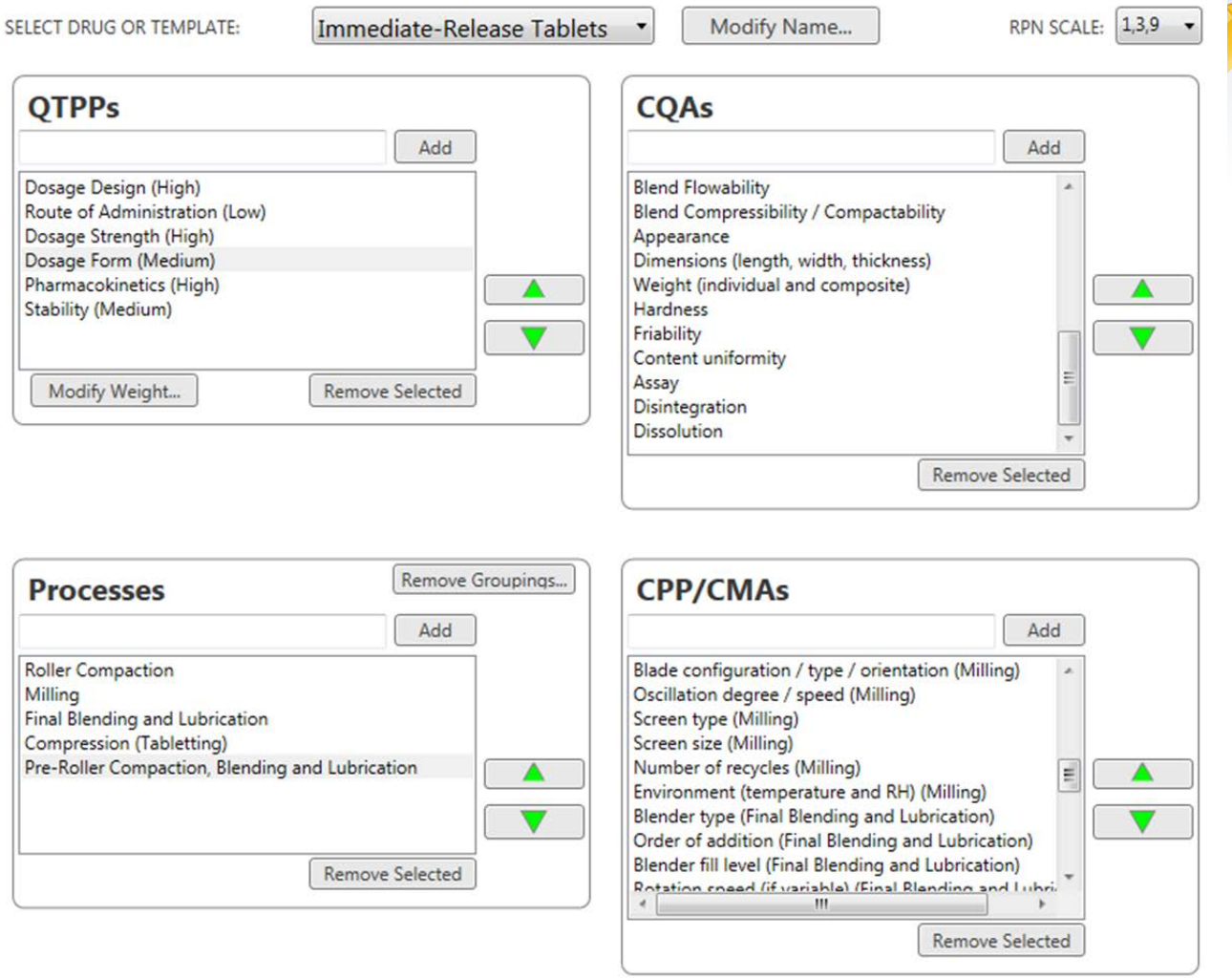
Project management



Risk Analysis

Re-usable templates.

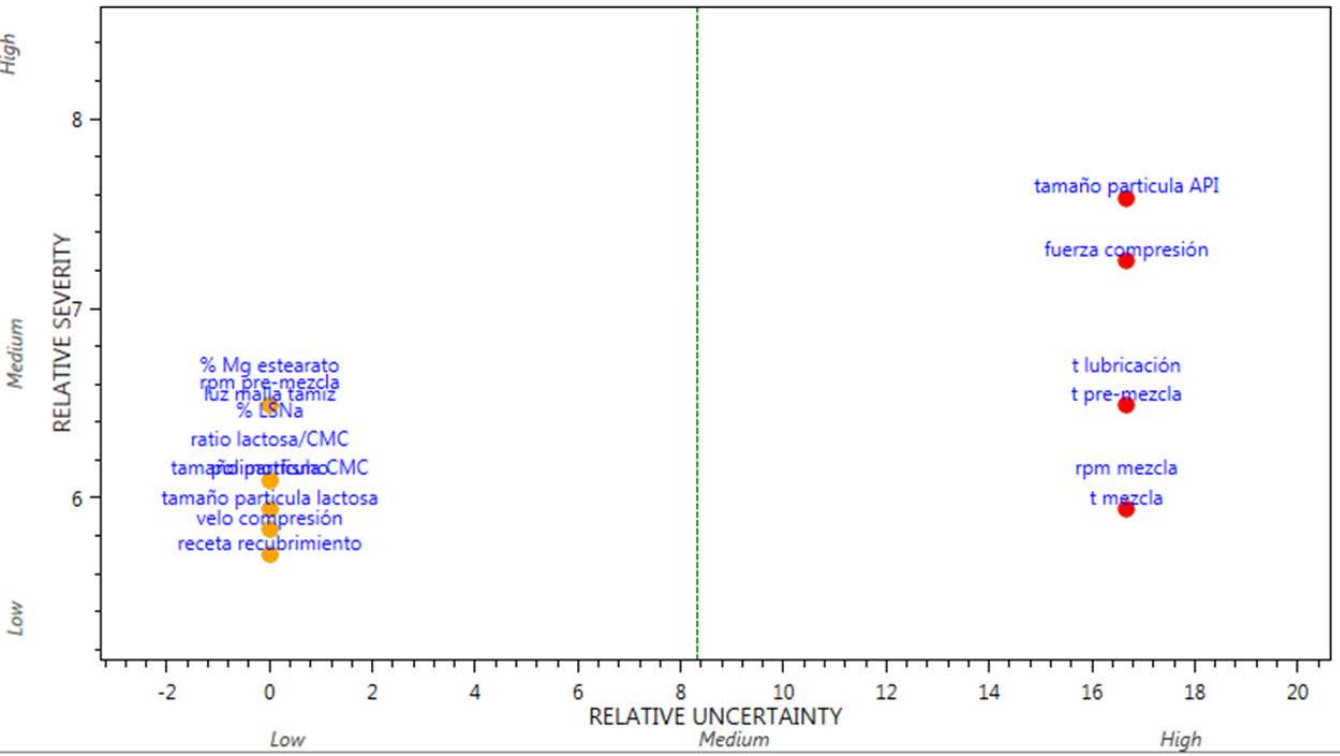
Collaborative environments to avoid endless meetings



Risk Analysis

Relative Uncertainty / Relative Severity

Right click the mouse and drag around to move the chart. Scroll the mouse wheel to zoom in and out.



Critical Cpps

High

- tamaño particula API (Process: Pre-mezcla)
- t pre-mezcla (Process: Pre-mezcla)
- t mezcla (Process: Mezcla)
- rpm mezcla (Process: Mezcla)
- t lubricación (Process: Lubricación)
- fuerza compresión (Process: Compresión)

Medium

- polimorfismo (Process: Pre-mezcla)
- luz malla tamiz (Process: Tamizado)
- tamaño particula lactosa (Process: Mezcla)
- tamaño particula CMC (Process: Mezcla)
- ratio lactosa/CMC (Process: Mezcla)
- % LSNa (Process: Mezcla)
- % Mg estearato (Process: Lubricación)
- rpm pre-mezcla (Process: Pre-mezcla)
- velo compresión (Process: Compresión)

Design of experiments

Pruebas OFAT retard

Pruebas OFAT retar
Fit Model 1h
Fit Model 4h
Fit Model 6h
Fit Model 3 juntas

Columns (9/0)
Prueba
tipo diluyente *
% diluyente *
tipo disgregante *
% disgregante *
dureza max *
disol 1 h *
disol 4h *
disol 10h *

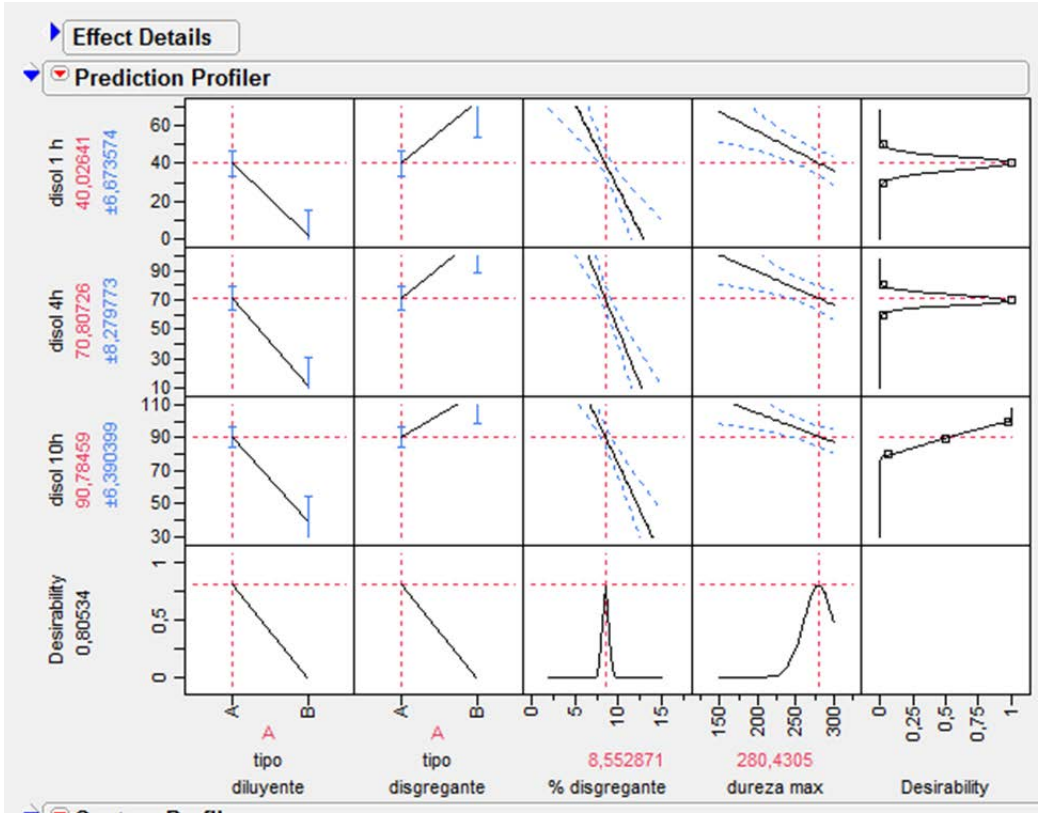
	Prueba	tipo diluyente	% diluyente	tipo disgregante	% disgregante	dureza max	disol 1 h	disol 4h	disol 10h
1	1	A	26,9	A	10	300	18,6	41,8	72,7
2	2	A	29,4	A	7,5	300	47,6	83,8	96,8
3	3	A	28,4	A	8,5	260	39,4	68,1	89,9
4	4	A	27,9	A	9	260	45,7	77,7	93,8
5	5	A	28,4	A	8,5	250	52,3	81,1	94,3
6	6	B	28,4	A	8,5	260	10,8	24,9	47,8
7	7	A	28,4	A	8,5	240	50,6	85,5	102,4
8	8	A	28,4	A	8,5	240	43,9	74,1	98,3
9	9	B	31,9	A	5	260	25,7	57	73,6
10	10	B	31,9	A	5	280	23,3	62,5	79,6
11	11	B	31,9	A	5	260	46	74,6	89
12	12	B	31,9	A	5	280	42,7	75,5	93
13	13	B	21,9	B	15	270	7,5	17,8	32,5
14	14	B	34,9	B	2	270	65,8	98,2	107
15	15	B	30,9	A	6	270	12	28,8	53,2
16	16	B	31,9	A	5	150	59,4	95,3	104,5
17	17	B	31,9	A	5	240	45	77,7	90
18	18	B	31,9	A	5	280	41,3	75,8	87,8
19	19	B	31,9	A	5	240	40,6	73,8	87,1
20	20	B	31,9	A	5	240	38,6	67,5	82,2

20 OFAT trials (not DoE)

Objective: use results to increase knowledge

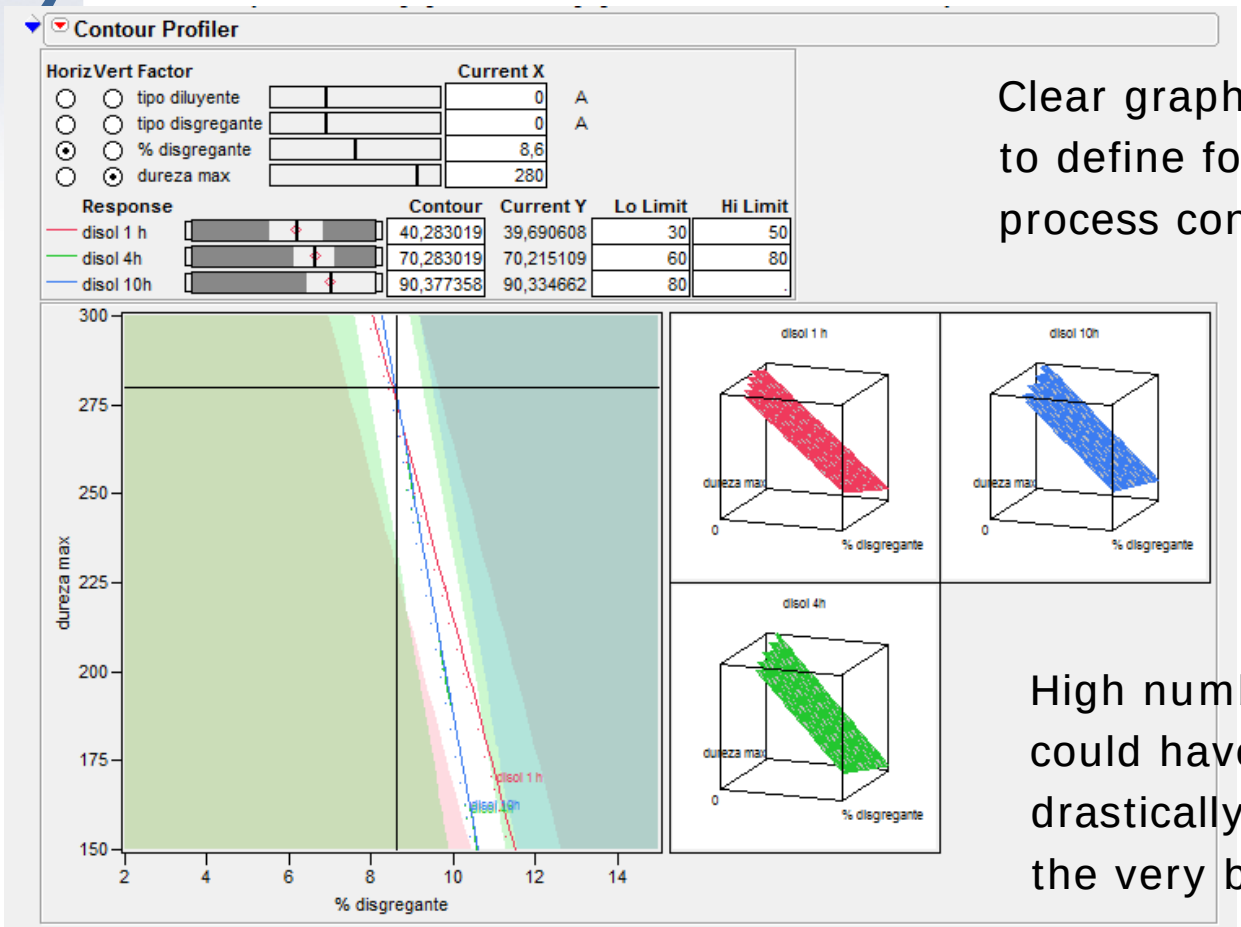
Modelling is it possible????

Design of experiments



A model is fitted from previous knowledge.
Critical variables identified.

Design of experiments



Clear graphic information to define formulation and process conditions.

High number of OFAT trials could have been reduced drastically applying DoE from the very beginning.

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