REDUCED SAMPLING
REDUCED TESTING

Carla Pina

Recipharm
good for business

HOW CAN WE

PANEL III	Moving Towards Better Efficiency Chair: Margarida Henriques | *Member of CCEIF-OF*

REDUCING SAMPLING AND TESTING?

Recipharm
good for business

PROCESS FLOW

How can we reduce the workload?

Recipharm
good for business

SAMPLING REQUIREMENTS – GMP GUIDELINES

Complete batch
Sampling all containers
Identity test on each sample

Deviation permitted with Validated Procedure
Sampling only a proportion of the containers

Composite sample
No details about the number of containers combined

Recipharm
good for business

SAMPLING REQUIREMENTS

FDA

- No requirements for the number of containers sampled
- Representative and a scientifically sampling plan must be used.

EMA

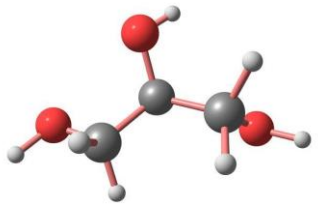
- Perform indentity testing on a statiscally representative composite sample (NIR analysis on every container)

Recipharm
good for business

SAMPLING REQUIREMENTS

FDA & EMA

- Require the testing of each container for identity and the limit test for Diethylene Glycol.



Glycerol

Recipharm
good for business

REDUCED TESTING DEFINITION

Not all parameters of the specification are tested. Only a reduced number of parameters are tested, while the other parameters are taken from the certificate os analysis from the manufacturer.

Recipharm
good for business

TESTING REQUIREMENTS

GMP Chapter 5

- Audited and qualified manufacturer that has been assessed and classified
- Manufacturer should have approppriate experience with the material
- ICH Q7 requires full testing on at least 3 batches

Recipharm
good for business

TESTING REQUIREMENTS

GMP Chapter 5

- Full analysis at ***appropriate intervals*** based on risk and compare the results with the material manufacturer or supplier’s certificate of analysis

Recipharm
good for business

REDUCED TESTING

Responsability

Pharmaceutical manufacturer

Parameters tested.

Supplier’s Audit

Reduced Sampling

Risk- based sampling plan

Recipharm
good for business

MANUFACTURING PLANT QUELUZ

- Finished Products: 213
- API: 175
- Excipients: 330

Recipharm
good for business

SUPPLIER QUALIFICATION FLOWCHART

How We Do It?

Recipharm
good for business

SUPPLIER QUALIFICATION

Good **confidence** on the Quality Management System

Responsabilities

Good **Quality** Material

Recipharm
good for business

Procedimentos Operacionais Padrão
SOP006.16

Autor :	Ramos Ana
Papel do autor :	Quality & Compliance Supervisor
Título :	Supplier Qualification
Data de fim :	01 Jul 2021
Estado :	Em vigor

Aprovação

Função	Papel	Assinatura necessária	Assinado por	Assinatura
	Proprietário	Ramos Ana	Ramos Ana	

Nível	Resultado	Data/Hora
1	Aprovado	29 Jun 2021 18:55

Notas

Função	Papel	Assinatura necessária	Assinado por	Assinatura
	Responsável do autor	Raposo Elvira	Raposo Elvira	

Nível	Resultado	Data/Hora
2	Aprovado	30 Jun 2021 15:49

Documentação impresso em: 05 Out 2022 15:07:39
Por: Pina Carla (CPINA)

Pág. 1/5

Recipharm
good for business

SUPPLIER RE-QUALIFICATION
(MONITORING)

Review of **Performance**

- Continued Monitoring Material Report (CMMR)
- Critical material attributes results
- Deviations
- Change controls.

Recipharm
good for business

Procedimentos Operacionais Padrão
SOP006.16

Autor :	Ramos Ana
Papel do autor :	Quality & Compliance Supervisor
Título :	Supplier Qualification
Data de fim :	01 Jul 2021
Estado :	Em vigor

Aprovação

Função	Papel	Assinatura necessária	Assinado por	Assinatura
	Proprietário	Ramos Ana	Ramos Ana	

Nível	Resultado	Data/Hora
1	Aprovado	29 Jun 2021 18:55

Notas

Função	Papel	Assinatura necessária	Assinado por	Assinatura
	Responsável do autor	Raposo Elvira	Raposo Elvira	

Nível	Resultado	Data/Hora
2	Aprovado	30 Jun 2021 15:49

Documentação
Impresso em: 05 Out 2022 15:07:39
Por: Pina Carla (CPINA)

Pág. 1/3

Recipharm
good for business

SAMPLING

Recipharm
good for business

RAW MATERIAL AND API SAMPLING RISK ANALYSIS

Scope

- Samples taken are representative of the batch.
- Risk value for each material based on several factors => ***Material segregation*** within the containers.

Recipharm
good for business

RAW MATERIAL AND API SAMPLING RISK ANALYSIS

APIs

- Total Identification
- Sampling of $\sqrt{n} + 1$

Excipients

- Total Identification or $\sqrt{n} + 1$ Identification
- Sampling of $\sqrt{n} + 1$

Recipharm
good for business

RAW MATERIAL AND API RISK ANALYSIS

A step by step decision process based on risk evaluation:

Identification

- Type of Container (Single use or multi use)

Evaluation

- Composite mix
- Potential for Segregation
- Sensitive/stable Materials

Mitigation

- Quantity/Intake
- Type of Process
- Function in formula

Recipharm
good for business

RAW MATERIAL AND API RISK ANALYSIS

Defined Actions for Existing Raw material and API codes

No need to perform sampling in several levels

In 2 batches, from 3 containers, 3 samples top, middle and bottom. Analysis on selected critical tests for potential segregation evaluation.

Recipharm
good for business

RAW MATERIAL AND API RISK ANALYSIS

Defined Actions for Newly Raw material and API codes

1 batch, from 3 containers, 1 sample from top and from 1 container top, middle and bottom. Analysis on selected critical tests for potential segregation evaluation.

2 batches, from 3 containers, 3 samples from top, middle and bottom. Analysis on selected critical tests for potential segregation evaluation.

Recipharm
good for business

RAW MATERIAL AND API RISK ANALYSIS

Final evaluation

A “Sampling Evaluation Report” is issued evaluating the obtained results.

No evidence of segregation - Sampling on the top of the container, for $\sqrt{n} + 1$ containers.

Evidence of segregation - Actions

Recipharm
good for business

RAW MATERIAL AND API RISK ANALYSIS

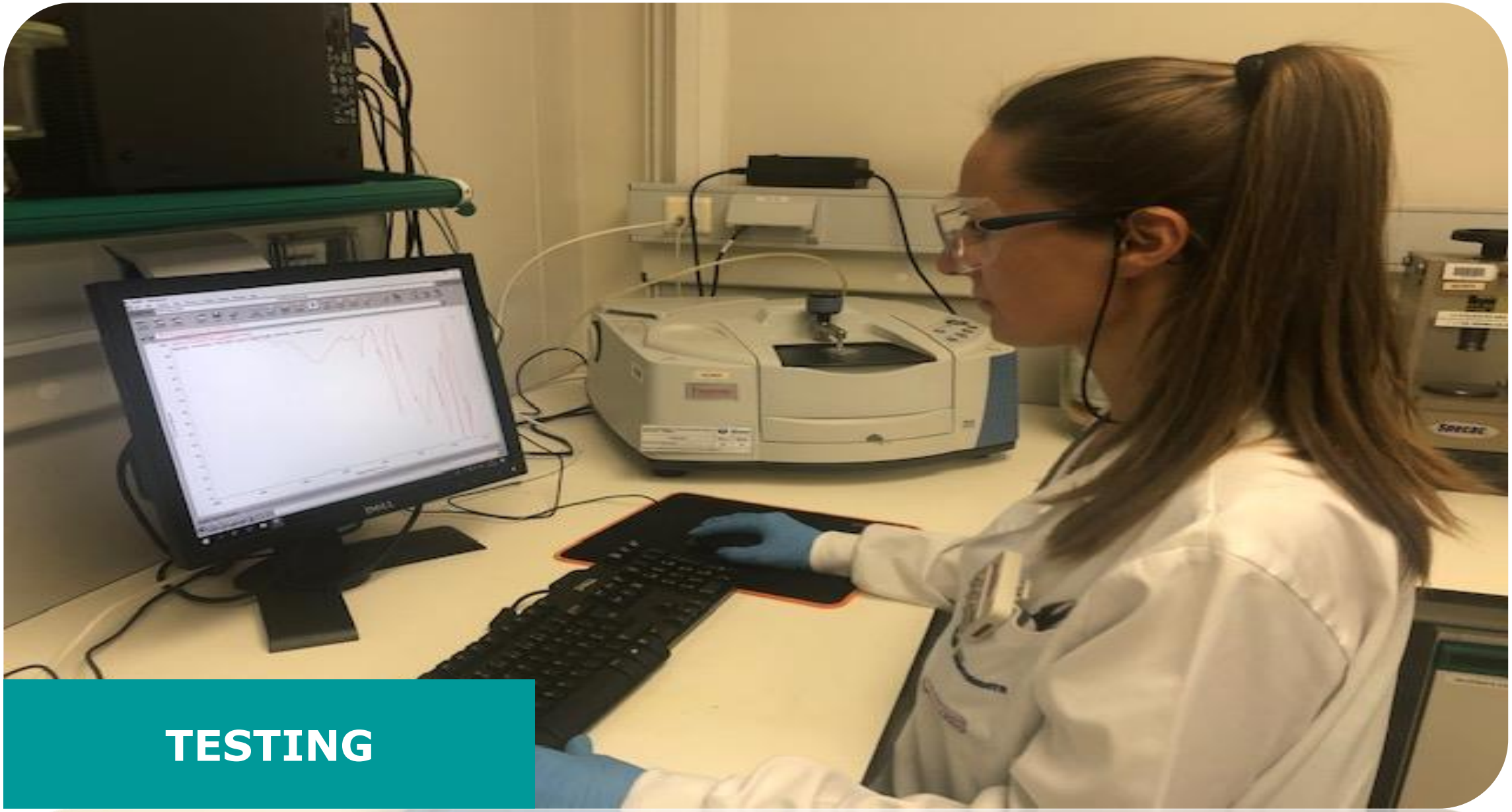
Risk Assessment Steps	Material Property		Risk Level 1 – Low 5 - high	RPN	Action For existing material	Action for new material
Risk Identification	Container	Single use	1	NA	Take samples from the top of container, following normal sampling plan	Low Risk Take 5 samples in 1 batch
		Multi use	5	NA	Continue to Risk Evaluation	
Risk Evaluation	Composite mix	Single component material	1	For API: RPN =1 Low Risk RPN ≥5 High risk For excipients: RPN ≤5 Low Risk	Low Risk Take samples from the top of container, following normal sampling plan High Risk Continue to Risk Mitigation	Low Risk Take 5 samples in 1 batch High Risk Continue to Risk Mitigation
		Composite or mixed material	5			
	Potential for Segregation	Homogeneous particle size distribution or micronized API	1			
		Not homogeneous or wide range of particle size distribution	5			
	Sensitive/stable Materials	Non Oxidisable / non Thermo-sensitive/ non Hygroscopic	1			
		Oxidisable/ Thermo-sensitive/ Hygroscopic	5			

Recipharm
good for business

RAW MATERIAL AND API RISK ANALYSIS

Risk Assessment Steps	Material Property		Risk Level 1 – Low 5 - high	RPN	Action For existing material	Action for new material
Risk Mitigation	Quantity/Intake For Raw Materials	Less than 30% of the formula	1	RMPN =1 Low Risk RMPN rate is ≥ 5 High Risk	Low Risk Take samples from the top of container, following normal sampling plan High Risk Take 9 samples in 2 batches	Low Risk Take 5 samples in 1 batch High Risk Take 9 samples in 2 batches
		Equal or more than 30% of the formula	5			
	Quantity/Intake For API	Equal or more than 30% of the formula	1			
		Less than 30% of the formula	5			
	Process	Solution/Granulation/Single Component	1			
		Suspension/Non Granulation	5			
	Function in formula (Excipients Only)	Others	1			
		Lubricants	5			

Recipharm
good for business

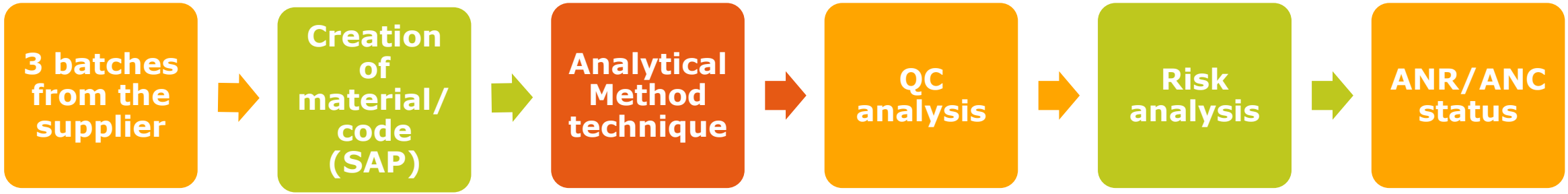


TESTING

Recipharm
good for business

REDUCED TESTING FLOWCHART

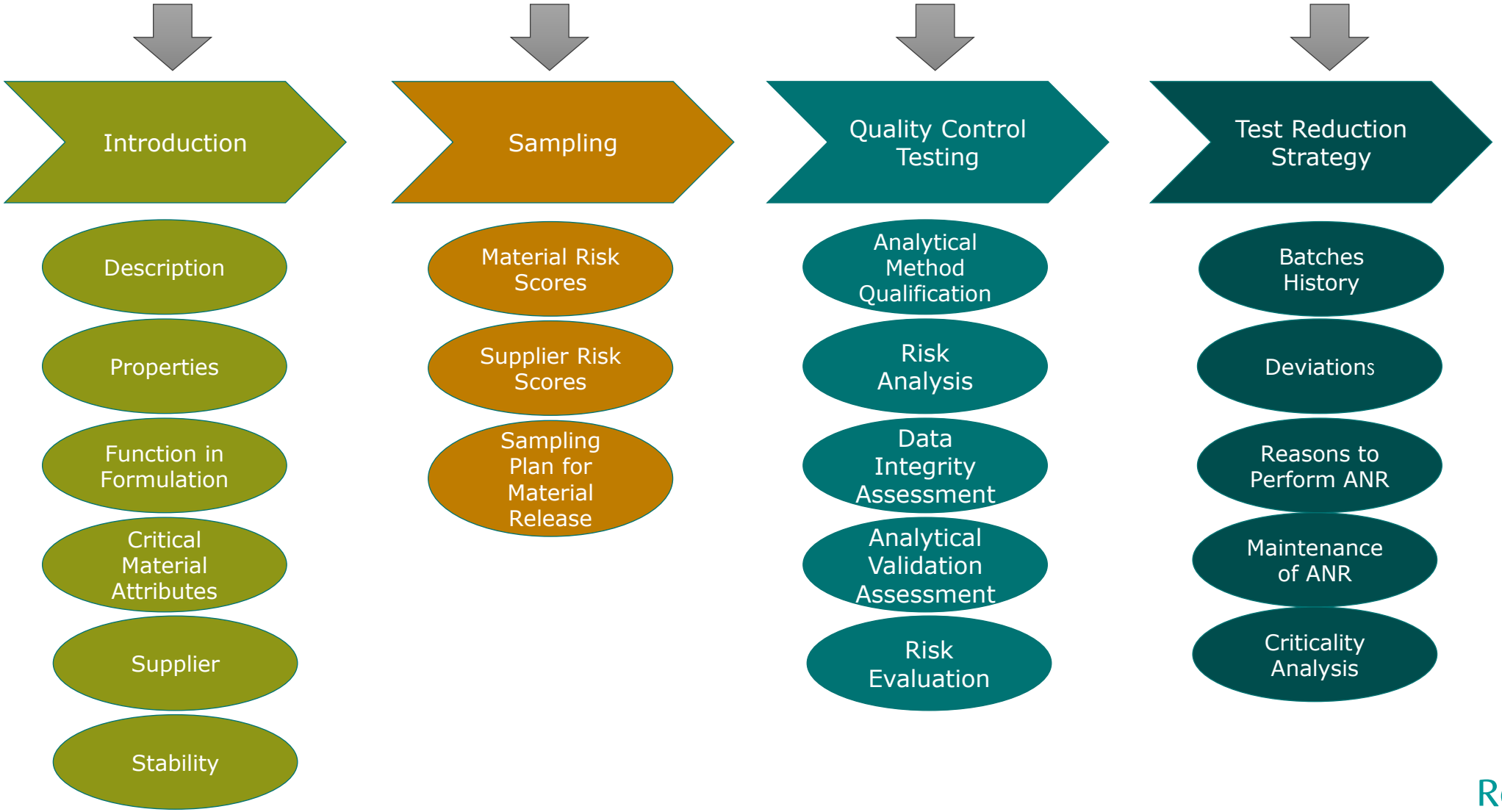
How We Do It?



Raw Material Risk Analysis

Recipharm
good for business

Raw Material Risk Analysis



Recipharm
good for business

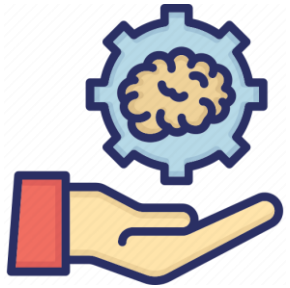
CRITICALITY ANALYSIS

Parameter (Tests)	Limit / range Hipercol Registration File	Direct impact in the CQA of the finished product?	Criticality for raw material	Criticality (Final conclusion)	Reduced analysis	Re-entry	Reanalysis	Comments (Justifications related to the test)
Appearance/ Description	Slightly yellowish, microcrystalline powder.	No	Yes	Critical	Yes	Yes	Yes	A change in appearance may indicate degradation or deterioration of the excipient, therefore this test is considered critical.
Solubility	Soluble in water, insoluble in alcohol.	No	No	Not Critical	Yes	No	No	Although this test is not considered a critical test with impact in the finished product critical quality attributes, it is an internal requirement not performed by the supplier, therefore it needs to be tested on ANR.
pH	6 – 8	No	No	Not Critical	No	No	Yes	Although not considered a critical test, according to the registration file, pH must be tested on reanalysis.
Loss on Drying	≤ 10 %	No	Yes	Critical	Yes	Yes	Yes	This raw material is hygroscopic, thus loss on drying is considered a critical test and needs to be performed always.
Viscosity	180 – 250 mPa·s	No	Yes	Critical	Yes	Yes	No	Viscosity test identifies the type of carboximethylcellulose sodium. Therefore, it must be performed on reduced analysis and re-entry.

Recipharm
good for business

REDUCED TESTING DEFINITION

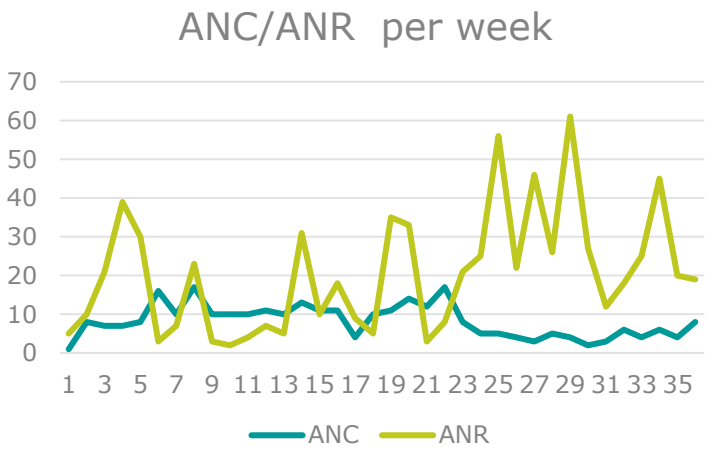
Risco Potencial	Potencial efeito(s) da falha	Severidade (S)		Controlo (C)		Probabilidade (P)		RPN (S x C x P)	Control / Mitigation Strategy
Não conformidade analítica do fornecedor não detectada pela Recipharm	Utilização de uma MP que não cumpre integralmente todas as especificações	7	Alta	2	Regular – detectado nos parâmetros críticos	2	Ocasional <5 lotes/ano	28	Risco baixo. Permite reduzir a frequência para ANC de 5 em 5 lotes (esta frequência será definida em função do histórico de lotes recebidos em anos anteriores).
				2	Regular – detectado nos parâmetros críticos	4	Repetido 5 a 20 lotes /ano	56	Risco moderado. Manter ANC anual (esta frequência será definida em função do histórico de lotes recebidos em anos anteriores).
				2	Regular – detectado nos parâmetros críticos	8	Regular >20 lotes/ano	112	Risco alto. Aumentar a frequência da ANC De 21 a 100 lotes/ano – ANC de 20 em 20 lotes >100 lotes/ano – ANC de 50 em 50 lotes (esta frequência será definida em função do histórico de lotes recebidos em anos anteriores).



< 5 lotes	ANC de 5/5 lotes
entre 5 e 20 lotes	ANC annual
entre 21 e 100 lotes	ANC 20/20 lotes
> 100 lotes	ANC 50/50 lotes

Recipharm
good for business

"QUICK WINS"



Productivity

Cycle Time

Release Batches

Keep it Simple

OBRIGADA!

carla.pina@recipharm.com

Recipharm
good for business