



# Risk-Based Approach to the Development of Novel Alginate Soft Capsules

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## Introduction

Magenta's Novel Alginate Capsules (NAC) technology involves an innovative process that produces seamless soft capsules with Alginate as the primary capsule shell component. The resulting capsules present enteric and anti-reflux characteristics. The NAC process is schematized in figure 1.

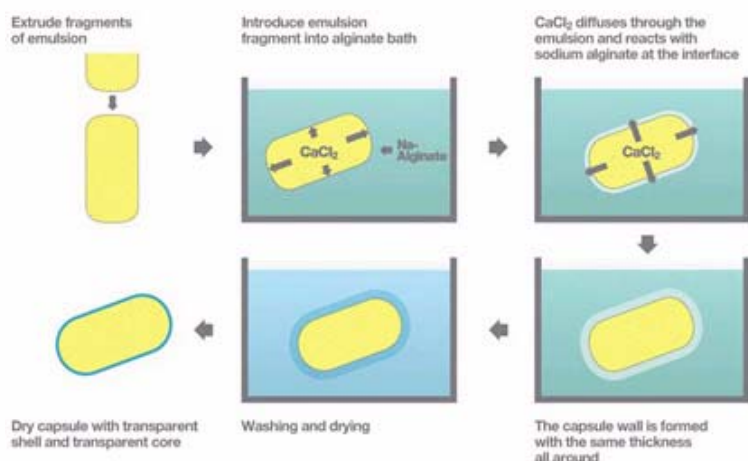


Figure 1 – Novel Alginate Capsules process

As outlined in the FDA's publication<sup>(1)</sup> development of new drug products and processes should follow the principles of Quality Risk Management. We have applied some of these principles (Quality by Design) and methodologies (FMECA)<sup>(2)</sup> to the early development of our novel oral dose form alginate capsule technology. Here we describe how these tools can be used to relate process improvements to the final quality attributes of the product.

## Method

Using FMECA, the first step was to identify all hazards and harms associated with each of the manufacturing process steps. The analysis process was completed by estimating the likelihood that the harm would occur and the severity of the resulting damage<sup>(3)</sup> using the severity, occurrence and detection tables shown in figure 2. The risk for each process step is finally analysed using the risk acceptability table.

The cutting step assessment is shown here (Fig 4) as an example of how FMECA analysis can be used to identify the influence of process parameters on a CQA (disintegration time). Disintegration times of NAC's (Fig. 5) made using either an automatic or manual cutting process

in EP and USP Phosphate buffers pH 6.8 were compared.

Detection Table		
Detection	Criteria	Scaling Factor
Almost impossible	Not detectable / visible	1
Remote	Detection with additional measurement / non typical IPC	0.75
Moderate	Easy to detect for operator / IPC	0.5
Almost certain	Automatic detection through compulsory 100 % testing	0.25

Severity Table		
Classification	Criteria	Occurrence Ranking
Catastrophic	Potential for death or serious injury to patient* or regulatory requirements violation or quality system violation	4
Severe	Potential for non serious injury or is critical to product quality	3
Moderate	Potential for patient annoyance or inconvenience or has non critical quality impact (e.g. cosmetic effect)	2
Negligible	Does not cause patient annoyance or inconvenience and does not affect product quality	1

Occurrence Table		
Classification	Estimated frequency of potential cause of failure	Occurrence Ranking
Frequent	≥ 10 %	4
Probable	1 to < 10 %	3
Occasional	0.02 < 1 %	2
Remote	< 0.02 %	1

Risk Acceptability Table				
Adjusted Occurrence	Severity			
	Negligible 1	Moderate 2	Severe 3	Catastrophic 4
Remote 1	GREEN	GREEN	GREEN	GREEN
Occasional 2	GREEN	GREEN	GREEN	ALARP
Probable 3	ALARP	ALARP	ALARP	ALARP
Frequent 4	ALARP	ALARP	ALARP	ALARP

Figure 2 – Ranking tables used to evaluate the risk for each of the NAC process step

## Results and Discussion

Major failure modes of critical to process parameters such as cutting speed were defined. These were shown to affect critical to quality attributes such as disintegration time and appearance.

The capsules made showed different disintegration times (fig.5).

The two processes differed in cutting speed and design and are illustrated by fig. 3. The manual cutting process resulted in "tail-shaped" emulsion fragments which created weak points on the shell (see fig.5 ) and ultimately faster capsule rupture during disintegration.



Figure 3 – Manual (left) and Automatic (right) processes

TOTAL RPN: 283														
ID1	Process Name or step	ID2	Potential Failure Mode	ID3	Potential Cause of Failure	Potential Hazard	Harm	Severity Occurrence Likelihood	Detectability	Adjusted Occurrence	Potential risk control measures			
P3	Cutting / shaping of emulsion fragments													
P3S2	Cutting of fragment using cutting disc: Speed: 500 rpm Wire thickness: 0.102 mm Wire length: 100 mm	P3S2B	Cutter speed too low	P3S2B1	Operator error	Omacor oil dose too high	Adverse reaction	4	2	0.5	1	ALARP	4	Calibrate cutter speed End product appearance testing 100 % shape inspection
						Deformed/impl capsule	Adverse reaction	2	2	0.5	1	BAR	2	
						weak capsule	No treatment	3	2	0.5	1	ALARP	3	
				P3S2B2	Speed not calibrated	Omacor oil dose too high	Adverse reaction	4	2	0.8	1.5	INTOLERABLE	6	
						Deformed/impl capsule	Adverse reaction	2	2	0.5	1	BAR	2	
						weak capsule	No treatment	3	2	0.5	1	ALARP	3	

Figure 4 – Example of the risk analysis undertaken for the NAC gelling process step.

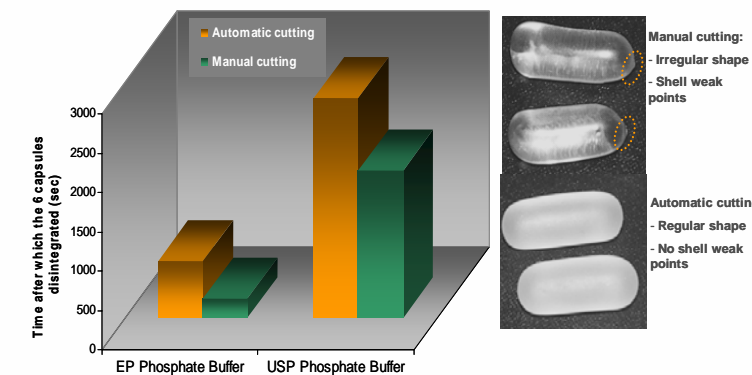


Figure 5 – Influence of the cutting process on the NAC disintegration time

## Conclusion

FMECA can be used in a number of ways to optimise process design and enable rational process control decisions based on product CQA's to be made during technology development.

This is however a living tool and requires frequent revision as the implementation of the risk control measures goes on.

## References

- 1) Department of health and human services – US FDA - (2004)– Pharmaceutical cGMPs for the 21<sup>st</sup> century – A risk-based approach – Final report.
- 2) ICH Expert working group – ICH Q9 guidelines – Quality Risk Management – 9<sup>th</sup> November 2005.
- 3) Mike W. Schmidt (2004) – The use and misuse of FMEA in Risk analysis – Medical Device Link.