

# CAPSUGEL®

## Challenges in Developing Stable and Efficient Probiotic Formulations

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# Summary

## Challenges in Formulating Probiotics

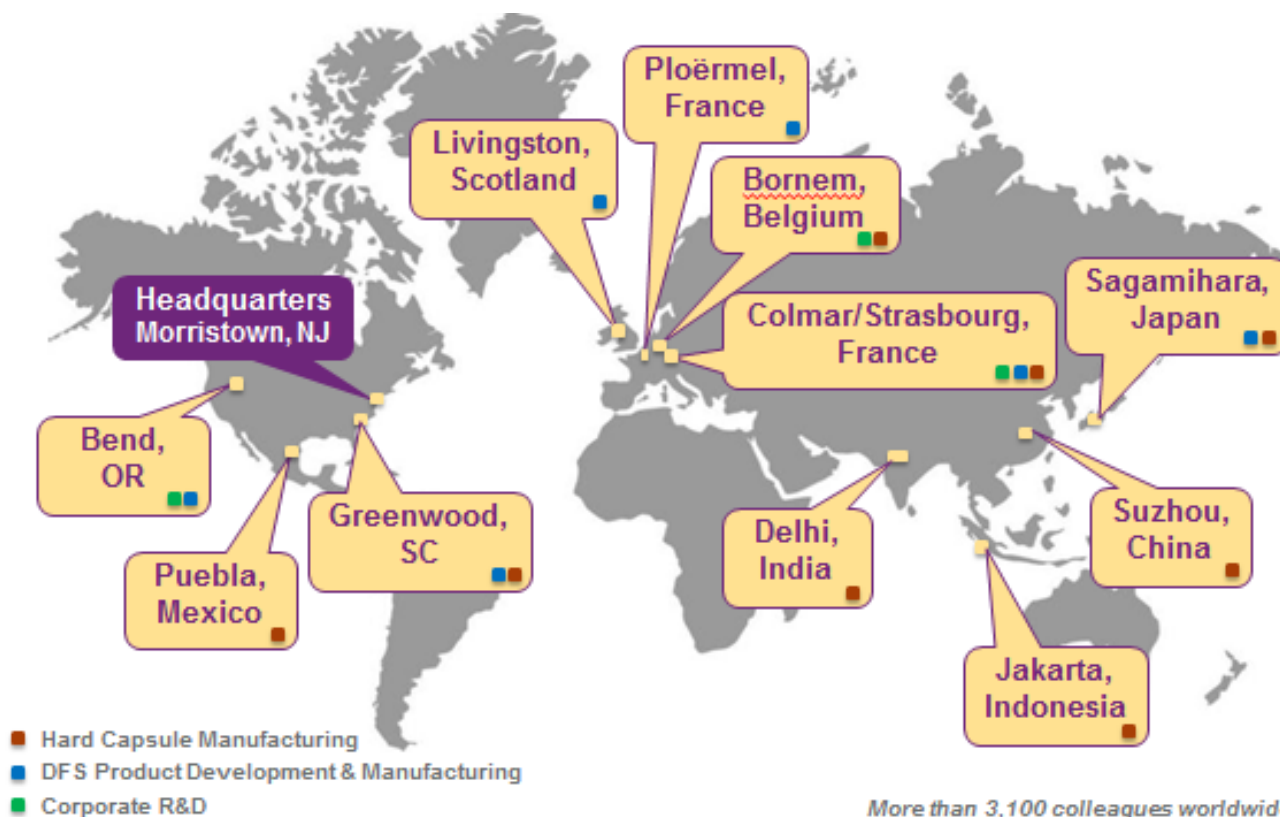
### Formulating Probiotics in Capsules

- Increase Shelf Life: Low moisture capsules
- Protection from Stomach acidity: DRcaps™
- Probiotics for Consumers with Swallowing Difficulties: Coni-Snap® Sprinkle Capsules
- Combination Products: DUOCAP™

### Conclusion

# Capsugel at a Glance

World's Leading Provider of dosage form solutions for Health & Nutrition, OTC, Generics, Specialty & Branded Pharmaceuticals



**# 1 hard gelatin and vegetarian capsule manufacturer**  
*Innovative, High-Quality, Products, Services, global scalability*



**Innovative drug-delivery technologies, specialized manufacturing, and a collaborative approach to address clients' most pressing product development challenges**



# Challenges in Formulating Probiotics

# Parameters Influencing Probiotics Stability

## **Probiotics have to pass two main hurdles:**

- Stability over shelf life
- Efficient delivery in appropriate site in the GI tract

## **Parameters influencing Stability:**

- Humidity
- Temperature
- Pressure/ temperature build up during tableting
- Coating stressful conditions
- Acid stomach conditions

**We will focus our presentation on solutions developed by Capsugel to efficiently formulate lyophilized probiotics**

# Formulating Probiotics In Capsules

# Major Challenges in Formulating Probiotics in Capsules

Challenges	Capsugel Solution
Maximum Shelf Life	Adapt water content of capsule to offer best conditions ensuring long shelf life.
Strain survival and efficiency	Specific capsule was developed to ensure passage of probiotics through stomach.
Specific needs of children and consumers with swallowing difficulties	Easy-to-open capsule for sprinkle usage on food without capsule swallowing.
Combination products	DUOCAP™: “2-in-1” capsules that allow effective delivery of combination products.



# Increase Shelf Life: Low Moisture Capsules



# Specialty Polymers: HPMC Capsules

Capsugel has developed HPMC capsule line with different film compositions.

## Vcaps® Plus Capsules

Composed of Pure HPMC  
and water  
with no additives  
Rapid dissolution  
at all pH



## Vcaps® Capsules

Composed of HPMC  
and a gelling agent  
Delayed dissolution  
at pH 1.2



## DRcaps™ Capsules

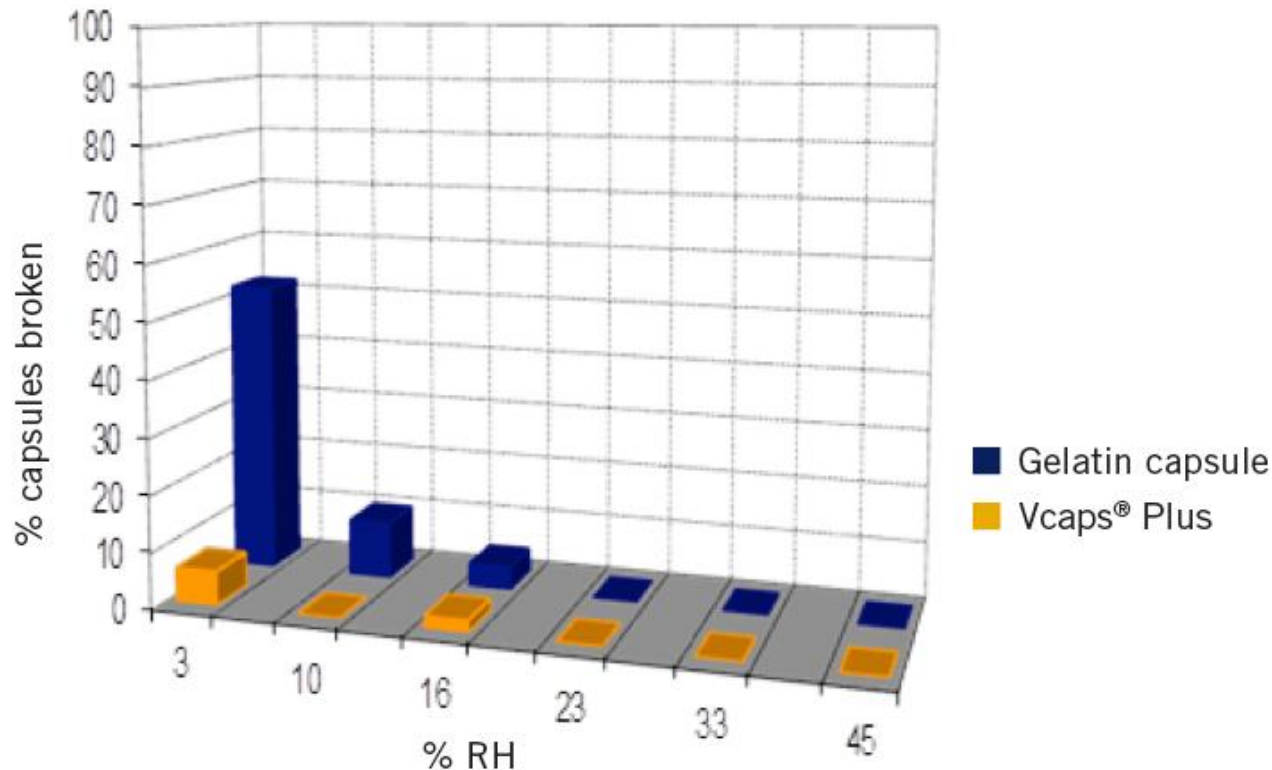
Composed of HPMC  
and Gellan Gum  
High resistance to  
dissolution at pH 1.2



# Mechanical Properties: HPMC Capsules

Gelatin capsules exhibit reduced mechanical resistance when water content decreases.

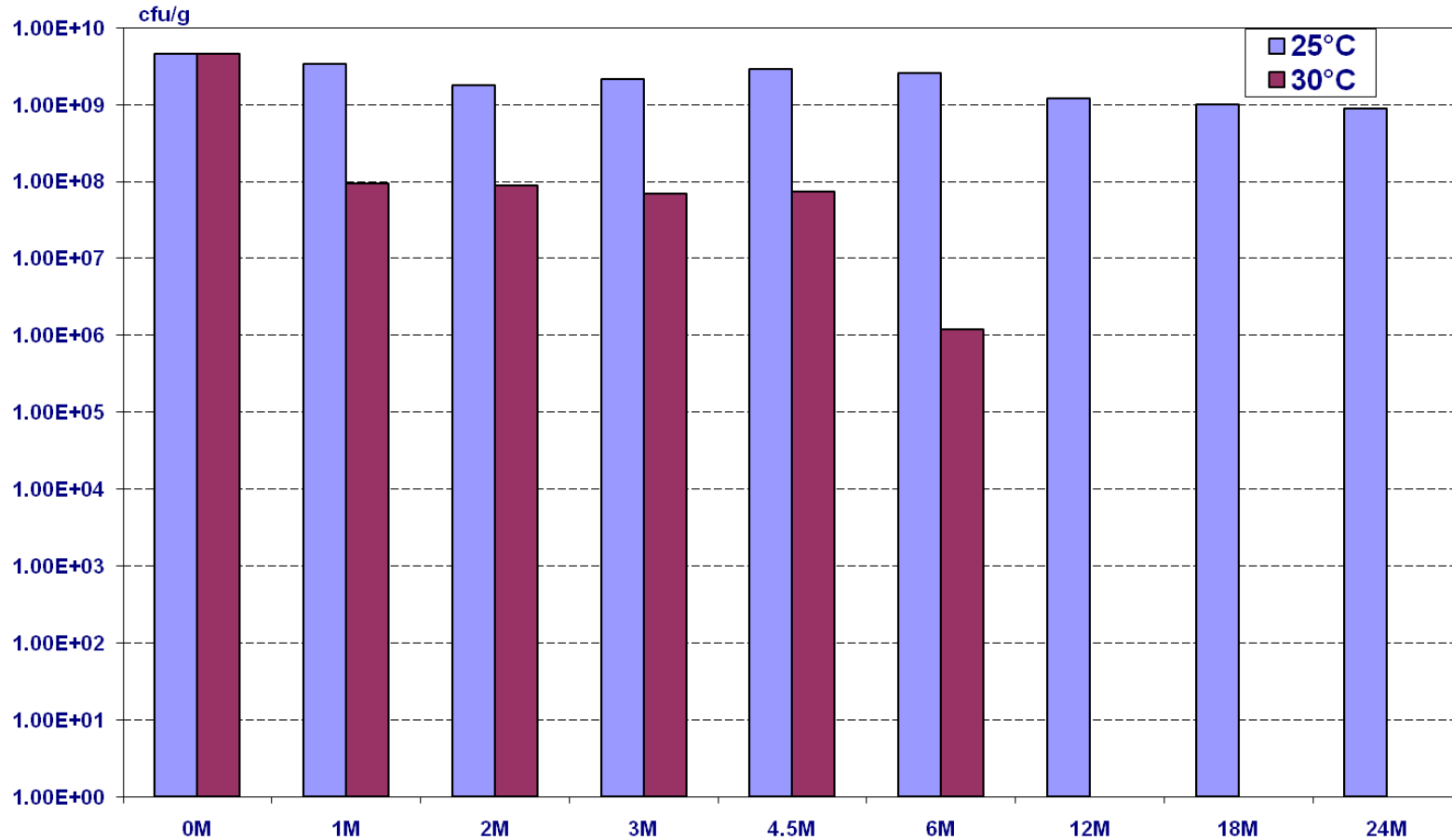
Standard HPMC have an increased mechanical stability at all humidities.



For probiotic application Capsugel's propose **low moisture HPMC** capsule enabling increased shelf life of finished product.

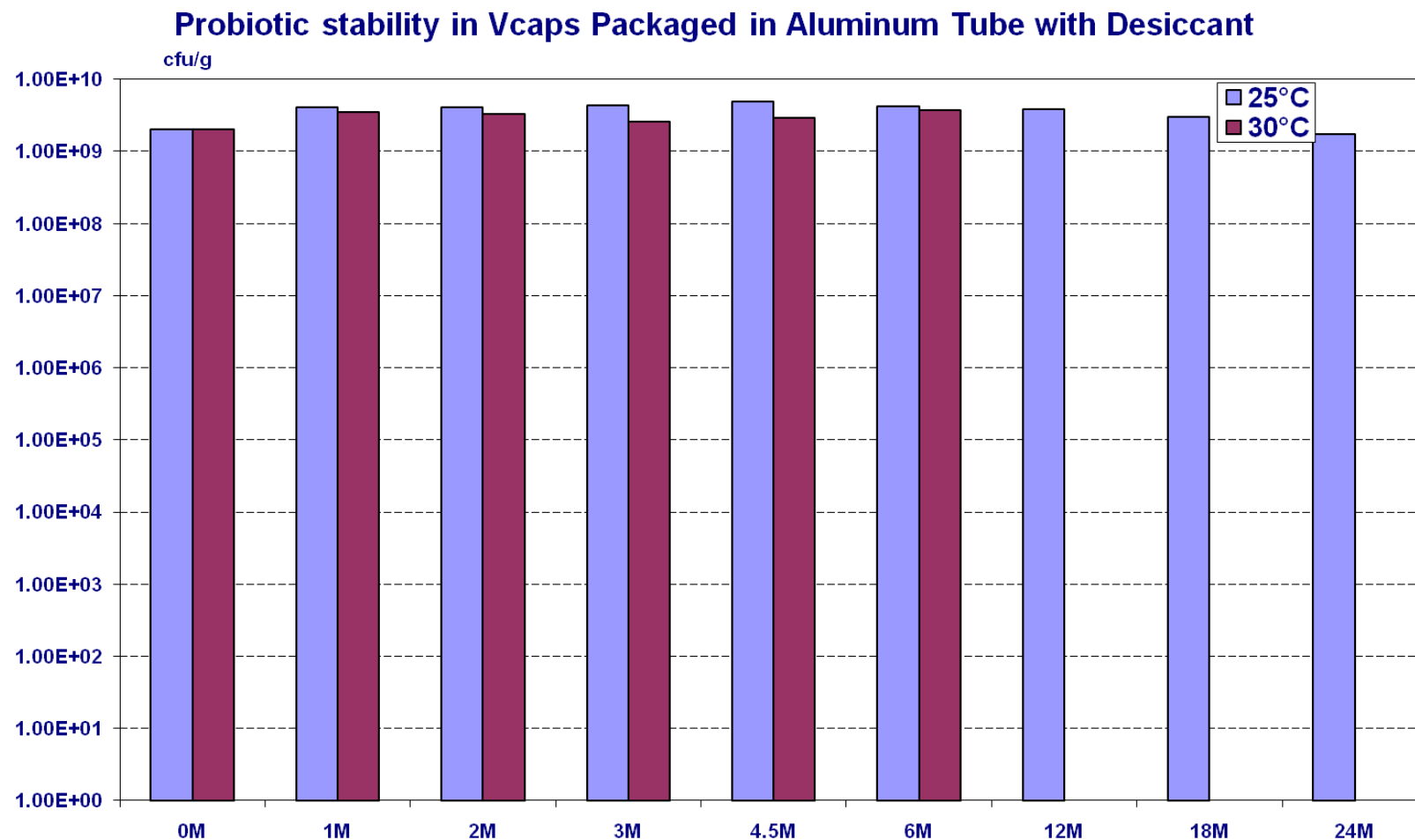
# Stability in Vcaps<sup>®</sup> Low Moisture Packed in Alu / Alu Blister

Probiotic stability in Vcaps Packaged in Blister



**High stability observed with Low Moisture HPMC up to 24 months minimum**

# Stability in Vcaps<sup>®</sup> Low Moisture Packed in Aluminum Tube with Desiccant



**High stability observed with Low Moisture HPMC up to 24 months minimum**

# Protection from Stomach Acidity: DRcaps™ capsules

# Composition of DRcaps™

## Composition:

- HPMC (Hypromellose) is produced from pine tree cellulose
- Gelling agent
- Water

## Properties:

- Capsule is resistant to dissolution in acidic media



# In-Vitro Tests

## Capsugel evaluated the resistance of DRcaps™ capsules to acidic media by different methods:

- In-Vitro Dissolution
- In-Vitro Disintegration
- In Vitro GIT Model, SHIME (Prodigest - Simulator of the Human Intestinal Microbial Ecosystem)

A novel hypromellose capsule, with acid resistance properties, permits the targeted delivery of acid-sensitive products to the intestine

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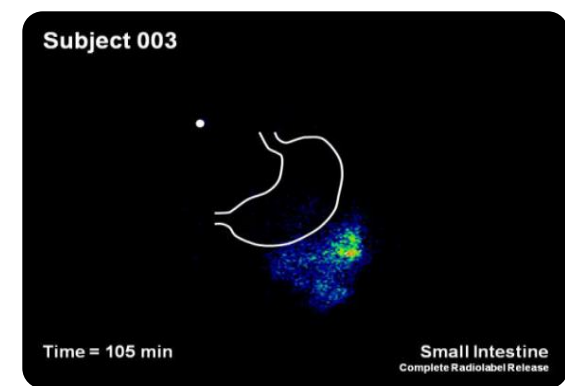
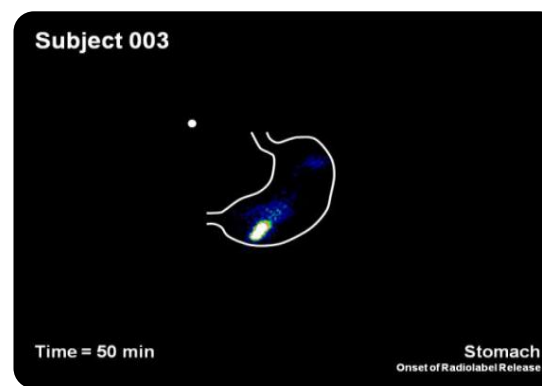
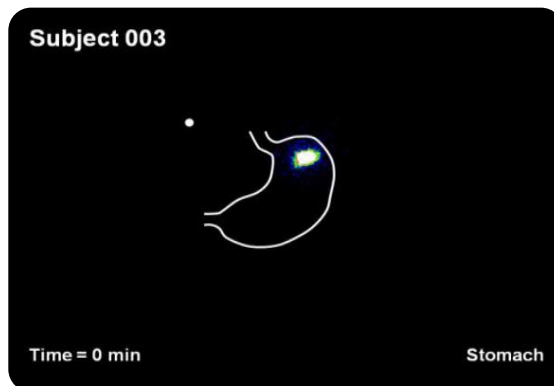
<sup>c</sup> Capsugel, 10 Rue Timken, 68027 Colmar Cedex, France

# DRcaps™ capsules: Acid Resistance – In Vivo

## DRcaps™ capsule Human Clinical Study (N= 8 subjects)

### Key Study Findings:

- DRcaps™ capsules displayed delayed release properties
- Disintegration started approximately 52 minutes after ingestion
- For the majority of subjects, complete release took place in the intestine
- Complete release occurred 20 minutes after the onset of release





Probiotics for Consumers with  
Swallowing Difficulties:  
Coni-Snap® Sprinkle Capsules

# Rationale for Developing Coni-Snap® Sprinkle Capsule

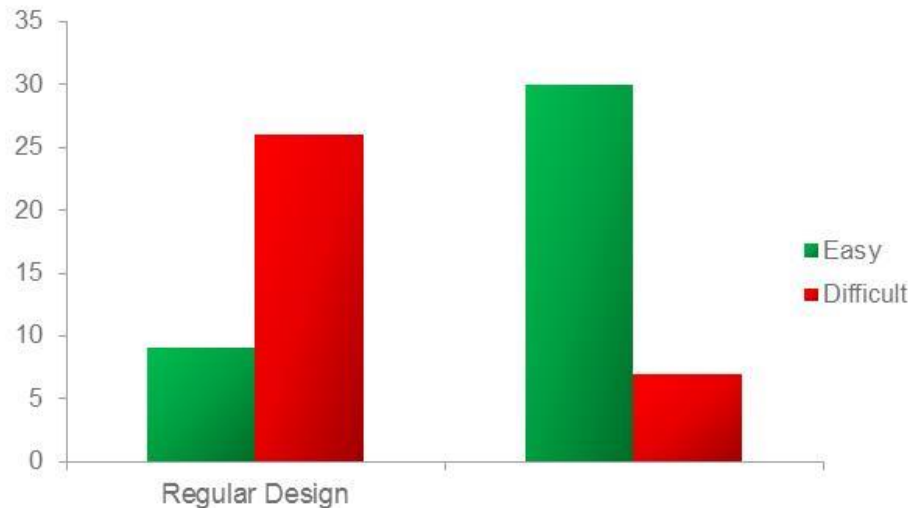
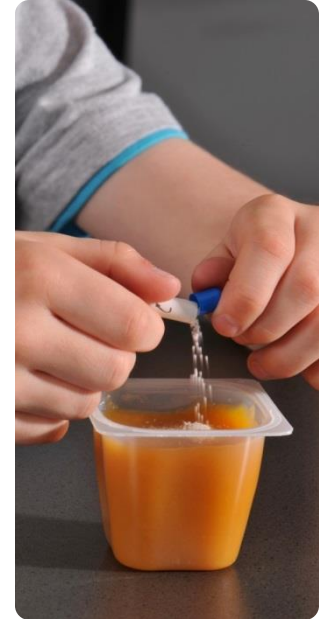
## Swallowing issues

- Affects 35% of the general population and 18%-22% of all persons in long-term care facilities
- 45% of institutionalized elderly and 36 % of adolescent report swallowing issues

## Coni-Snap® Sprinkle

### Evaluation of product performance by 37 participants in 2 panels

- Parents of young children
- Elderly individuals (over 80) and not impaired



81% of Participants found new design easy to open



Combination Products  
DUOCAP™ capsules

# DUOCAP™ Probiotic capsule

## DUOCAP™ technology creates an internal barrier to prevent water migration in probiotic internal capsule:

- Perfect for moisture sensitive compounds: Glycerol in external capsule prevents water absorption in internal capsule
- Designed to improve stability and facilitate delayed release
- Internal capsule can be DRcaps™: delivers probiotic in intestine
- Could allow second ingredient to expand health claims (e.g. Vitamin D)



# Proof of Concept

Inner capsule Vcaps® Plus  
size 3  
Filled with 100% Probiotic



Filled in outside Vcaps® Plus  
size 00  
Containing glycerol



## Storage conditions:

- 4-8° C and 25° C/60% RH

Storage conditions	T0	T 1M	T 2M	T 3M	T 6M	T 9M	T 12M	T 18M	T 24M	T 36M
4-8°C	X	X	X	X	X	X	X	X	X	X
25°C/60% RH		X	X	X	X	X	X	X	X	X

## Packaging:

- PP bottle (no desiccant)

## Tests performed:

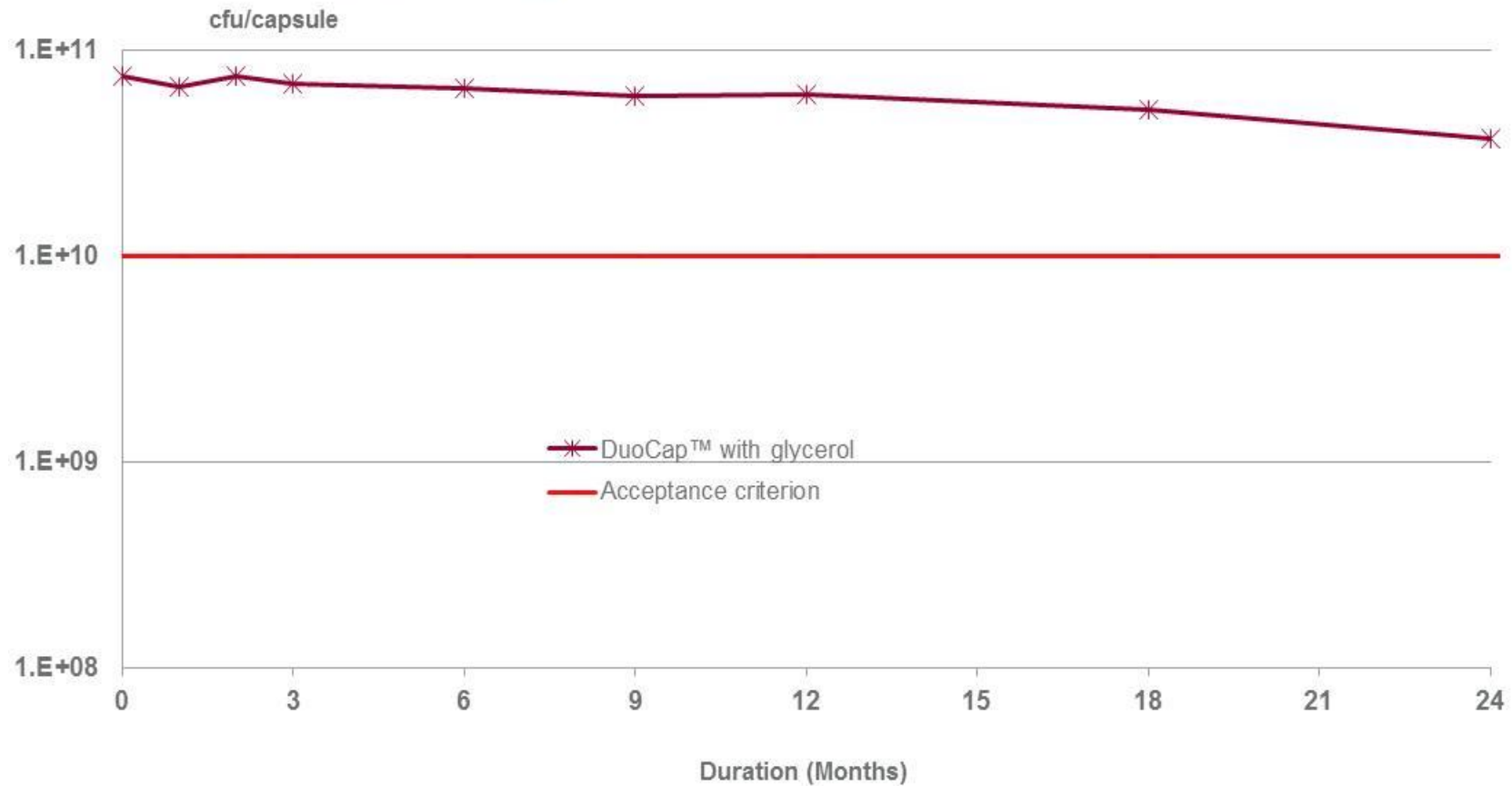
- Total count viability performed by Capsugel QC department in Colmar

## Latest results:

- **Stability confirmed after 24 months at 25C/60% RH for DUOCAP™ with glycerol in outer capsule**

# Stability Results





## Stability of Probiotic in Glycerol DuoCaps filled in PP bottle stored for 24M at 25°C/60%RH



**Stability Study confirmed stability of probiotic in DUOCAP™**

# Conclusion

# Capsugel's Probiotic Portfolio

Solutions	Applications	Polymer
	<p>Increased shelf life can be obtained with low moisture HPMC capsule</p>	<p>HPMC Low Moisture</p>
	<p>Survival and efficiency: probiotics are protected and delivered to intestine</p>	<p>HPMC</p>
	<p>Alternative to Sticks and Sachets, Solves swallowability issues</p>	<p>Gelatin and HPMC</p>
<p>DUOCAP™</p> 	<p>Synergy enhancement, efficacy in protecting probiotics in presence of other actives</p>	<p>HPMC</p>





CAPSUGEL®