

# Capsugel<sup>®</sup>

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## Cultivate Your Probiotic Performance: Market Trends and Innovative Solutions





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## Cultivate Your Probiotic Performance

Consumers are quickly adopting supplements to maintain their well-being in an effort to keep their health care costs down. Between 2014 and 2015 alone, global supplement sales grew an impressive 8 percent to \$88.3 billion, with continued increases anticipated, according to the global market research company, Euromonitor International.

Probiotic supplement use is expected to ride along this wave of growth. Currently, global sales for probiotic foods such as yogurt and sour milks (\$41 billion in 2015) far outweigh that of probiotic supplements (\$3.8 billion). However the consumption gap is projected to narrow in many parts of the world.

This trend will occur as consumers and health care providers become more aware of the numerous health benefits of probiotics beyond digestive health and the various delivery forms that are more convenient and effective than food and drinks. Marketing is the key component to the retail growth of probiotic supplements. Understanding what consumers want and who influences their purchases will be critical for probiotic manufacturers, brands and retailers.

To provide insights into the global probiotics market, this report analyzes regional trends and explores how consumer education, government regulations, probiotic forms, wellness claims and effective delivery systems can help cultivate probiotic performance in the coming years.

## Top Countries in Probiotic Supplements

Five countries represent a combined 77 percent share of the global retail sales of probiotics—the United States, Italy, Japan, Russia and Taiwan. Scientific evidence to support claims and development of specialty strains to improve targeted action, the introduction of new delivery forms along with increased consumer awareness all are expected to contribute to the global growth of probiotic sales during the next five years.

## Regional Analyses from Euromonitor International

### THE AMERICAS – KEY TRENDS

Probiotic supplements generated a retail value of \$1.9 billion in the Americas in 2015.

**North America** is the world's most progressive market, as consumers prefer their targeted action and more immediate health effect. The retail value of probiotics totaled \$6.1 billion in 2015, with probiotic supplements holding a strong 30 percent share.

The retail value of probiotics in **Latin America** is a little more than half the value of North America at \$3.7 billion; however, probiotic dairy-based yogurt dominates the market at 96 percent. Probiotics typically are recommended by health care practitioners for certain medical conditions as an antibiotic treatment or for gastrointestinal problems. Supplements are not widely available and, in some cases, not approved as an over-the-counter product or nutritional supplement. Nevertheless, probiotic supplements are projected to grow 8 percent in the next 5 years, compared with an expected 15.6 percent growth for probiotic yogurt. An increased demand for probiotic supplements will hinge on regulatory agencies allowing over-the-counter sales.

**3.8**  
**BILLION**

US \$ retail value of  
probiotic supplements  
in the world 2015

**7.8%**  
**RETAIL VALUE**

increase from 2014

**37%**  
**EXPECTED**  
**GROWTH**

by the year 2020

*Source: Euromonitor International*

## EMEA – Key Trends

The most progressive market for probiotic supplements is Western Europe, which shows a 14 percent market share compared with 9 percent in Eastern Europe and only 1 percent in Africa and the Middle East. Accessibility, affordability and dispensing practices all play a critical role in the market dynamics of these regions.

In **Western Europe**, there are future opportunities for probiotic supplements due to a change in the region's regulatory climate. In 2009, the European Food Safety Agency (EFSA) and other regulators began reviewing the digestive health claims of probiotic dairy-based yogurt and eventually banned them. As a result, the retail value of probiotic supplements grew at a steady pace and the consumption gap narrowed between probiotic foods and probiotic supplements in 2015 to \$3.7 billion—a decrease of \$1.3 billion from its peak in 2009.

In **Eastern Europe**, probiotics have suffered a regulatory backlash in recent years, but a long-standing acceptance of probiotics among this region's consumers, coupled with stronger recommendations from health care practitioners, is expected to contribute to strong growth of probiotic supplements here. Supplements are projected to grow at the fastest rate of 23 percent in the next 5 years, compared with a decline of 4.6 percent for probiotic yogurt.

In the **Middle East and Africa**, Probiotic supplements are anticipated to grow at the fastest rate over the next five years at 126 percent, given its relatively small share of the market at this time.

## Asia Pacific – Key Trends

In Asia Pacific, which includes countries such as **Japan, China, India** and some countries in **Central and Southeast Asia**, there is a strong demand for probiotic supplements—specifically probiotic drinks.

Probiotic supplements in this region are mostly defined as a medicinal product with regulatory restrictions like prescription drugs that prevent their purchase in the typical retail environment. These market limitations will prevent a strong growth of supplements here in the next five years, although some alternative marketing opportunities could exist with the medical community and regulators.

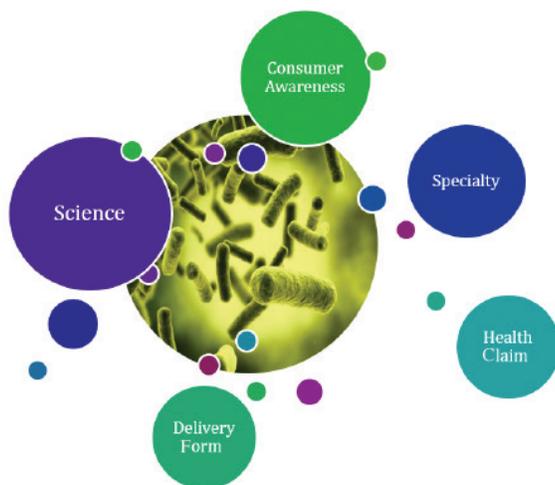
Australia and New Zealand are more progressive markets for nutritional supplements, offering innovation in formulations such as confectionary or whole-food supplements that complement a new natural healing trend that dominates that part of the world.

## New Discoveries Bring New Retail Opportunities

In addition to their century-long treatment for diarrhea caused by antibiotics intake, probiotics now are being developed for skin health, oral health, immunity boosting and respiratory health beyond hospital use to athletes experiencing a change in their gut microbiota due to stringent diets to improve fitness. There are increased applications for managing irritable bowel syndrome and inflammatory bowel disease.

New possibilities also exist with research and studies on managing the health of gut microbiota as it relates to metabolism and weight and of the brain-gut axis related to cognitive health and the role of toxins in the gut that might affect cardiovascular health.

### Drivers of innovation



Source: Euromonitor

Formulations are evolving to include Kosher and Halal probiotics, time-release options, combinations with other ingredients for added health benefits, sugar-, dairy- and allergen-free options and professional lines endorsed and sold by health care practitioners, naturopaths and dietitians.

Research in 2015 by Capsugel with gastroenterologists revealed that about 85 percent discussed probiotics with patients, but in many cases did not have specific recommendations on brand, strength or frequency of use. The probiotic industry clearly has an opportunity to provide appropriate guidance to various practitioner groups.

## Influencers Are Shaping Future Trends

Marketing is the key component to the retail growth of probiotic supplements, and understanding who influences probiotic purchases is critical for any marketing initiative.

Health care practitioners, for example, must be more aware of the benefits of probiotics in all therapeutic areas. Pharmacists, through recommendations, are also key drivers of sales. Online health advice and social media are huge awareness generators in today's world as consumers engage with industry and brand experts.

The issue will be controlling the veracity of the information being disseminated. In Brazil, for example, there are video games to educate children on good digestive health habits that show probiotics as a way to fight the enemy in the gut. There are health apps and personalized lifestyle programs being launched by brands that include the correct use of that brand's probiotics for a specific health claim.

## Market Research Reveals New Age Wave

Ongoing consumer research by the Natural Marketing Institute (NMI) indicates a new age wave, known as Millennials, are using vitamins, minerals and supplements at about the same level as Baby Boomers. Millennials represent a population slightly larger than the Baby Boomer generation, which has driven the age wave for the last two decades and will continue to be a group of heavy users of supplements.

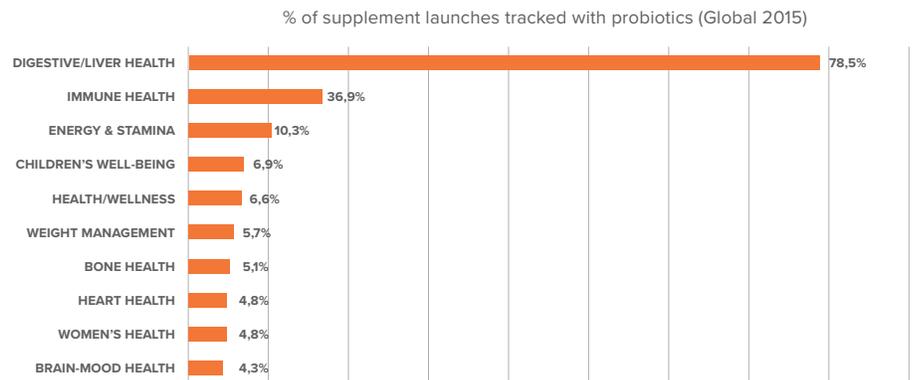
National Marketing Institute's Supplement OTC Rx Database (SORD) 2015 study confirms that self-directed health care is in the forefront for all generations, and consumers have a strong understanding of how to achieve healthy aging. In addition to eating healthy, exercising and seeing a doctor, taking vitamins and supplements now has reached 77 percent. Moreover, consumers are gaining awareness of probiotics, with 20 percent of surveyed consumers reporting they do not feel that they are getting enough in their diets. Gen Xers and Baby Boomers show the greatest desire for having probiotics integrated into their diets.

## Probiotics Spread to New Health Categories, New Claims

More than three-quarters of new supplement launches with probiotics have a digestive health claim, followed by immune health, according to a 2016 study by Innova Market Insights.

The Age Waves		
Terminology	Age as of 2015	Current users of VMS
Millennials	17-38	34%
Gen X	39-50	12%
Boomers	51-69	43%
Matures	70+	11%

### Top 10 health positionings for supplement launches with probiotics global 2015



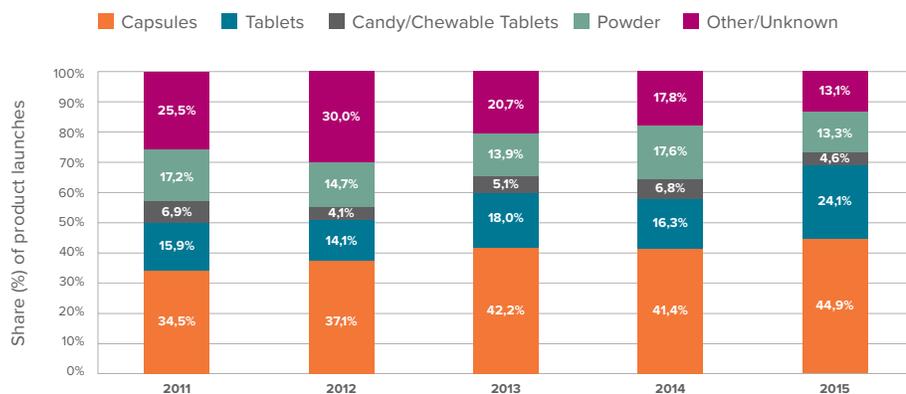
*Innova Market Insights, 2016*

However, several other areas represent growth opportunities, including energy and stamina, weight management, bone health, heart health and brain-mood health.

There are more strains today than ever. Although half of all probiotic supplements launched in 2015 contain the typical *Lactobacillus acidophilus* and *bifidus*, some secondary strains are emerging. Interestingly, the majority of new products contained several different probiotics.

The Innova study also revealed that nearly 45 percent of supplement launches with probiotic ingredients came in a capsule, an increase of more than 10 percent from 2011 to 2015, with a strong trend toward vegetarian capsules. Probiotic capsules introduced in 2015 each tout varying benefits.

### Capsules continue to grow as the choice of probiotic delivery



Innova Market Insights, 2016

## Understanding Consumer Needs Is Key to Market Opportunities

A real need in the digestive aid category is for differentiation. About one-third of probiotic users are searching for a product to manage or treat a specific health issue, followed by 23 percent who are concerned with the number of bacteria present in the product, then 23 percent interested in the strain of the bacteria.<sup>1</sup>

Digestive enzymes appear to be a niche opportunity. About 77 percent of the consumers who are using digestive enzymes are using them to treat digestive issues, but digestive enzymes don't even register as one of the key supplements used by digestive managers.<sup>1</sup>

The number-one-prescribed probiotic in Brazil, for example, is a dual capsule that contains a solubilized prebiotic in the outer shell and a probiotic in the inner shell.

Prebiotic-probiotic combinations and other vitamin/mineral supplement combinations also present opportunities.

## Challenges in Formulating Probiotics

There are two main hurdles in formulating probiotics—the stability over shelf life and efficient delivery of the probiotic to the appropriate site in the gastrointestinal tract. Capsules continue to grow as the preferred choice for probiotic delivery.

Stability is influenced by storage humidity, dosage form, moisture content, temperature, pressure and temperature buildup during the tableting process, solvent use and drying conditions during enteric coating process and acidic stomach conditions.

<sup>1</sup> Source: Natural Marketing Institute, SORD 2015

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 powder and liquid combinations (like a probiotic in the inner capsules and a solubilized prebiotic in the outer capsule).

Low-moisture capsules and acid-resistant capsules are effective ways to maximize shelf life and delay delivery to the GI tract. Capsugel offers a portfolio of capsules that solve these issues through different technological applications.

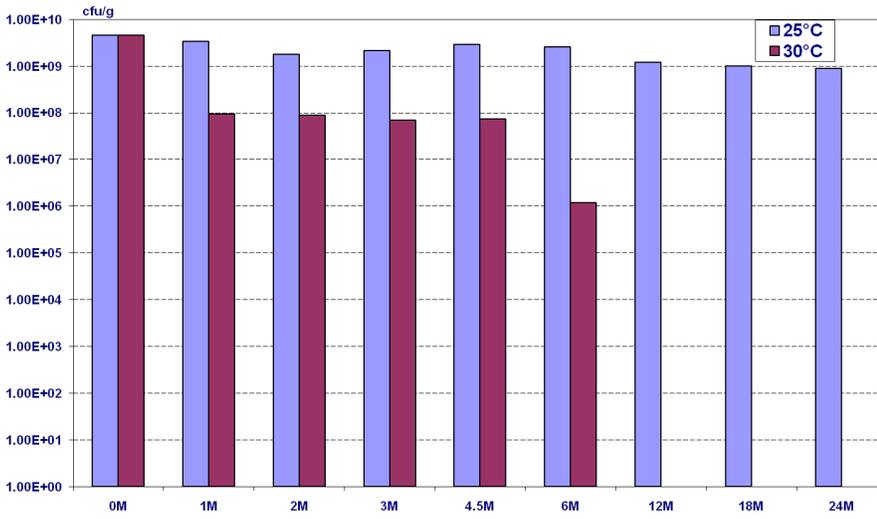
## Low-moisture Hypromellose (HPMC) Capsules Improve Probiotic Stability

For more than 100 years, capsules were only made with gelatin. Consumer demand for alternatives to animal products and the need for more technically advanced products led to the development of hypromellose (HPMC) capsules. Gelatin capsules typically contain 13 to 16 percent moisture for shell pliability and functionality of the capsule. After filling, the capsule equilibrates with the fill material, and capsule moisture can transfer into the probiotic. This may cause premature activation of the probiotic and cause brittleness of the gelatin capsule shell. Many manufacturers overfill or increase the size of their product to offset loss in potency due to moisture transfer. This can lead to significant increase in the cost of the final product.

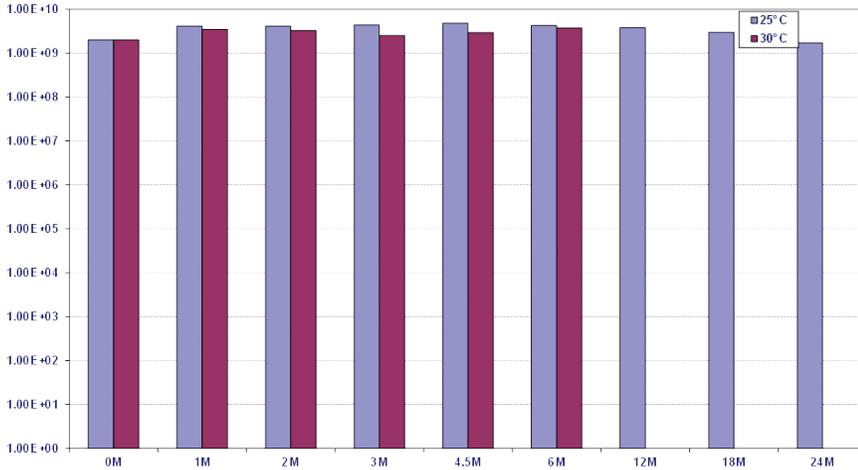
Capsugel has a specialty polymer line of capsules in HPMC, a plant-based material, to address a variety of different challenges with probiotics. HPMC capsules have a low water content—between 3 to 9% and can be lowered to <2.5%, achieving a water activity of <0.24. At that level, hygroscopic ingredients cannot pull moisture from the shell—thus the capsule maintains its mechanical resistance. The full line of HPMC capsules from Capsugel, including Vcaps® Plus, Vcaps® and DRcaps™, are available at this lower moisture level.

In a stability study of a Vcaps low-moisture capsule packaged in an aluminum-aluminum blister, the capsule’s moisture level was <2.5%. At 25° C, or about 76° Fahrenheit, the product remained stable throughout a 24-month period, which is an indication of a shelf life that can extend to 36 months. This was confirmed with an identical stability study of a Vcaps low-moisture capsule packed in an aluminum tube with a desiccant, shown on the following tables.

Probiotic stability in low-moisture Vcaps® packaged in Alu/Alu Blister



Probiotic stability in low-moisture Vcaps® packaged in Aluminum tube + desiccant

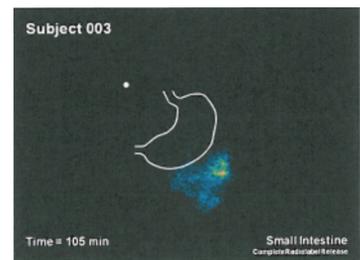
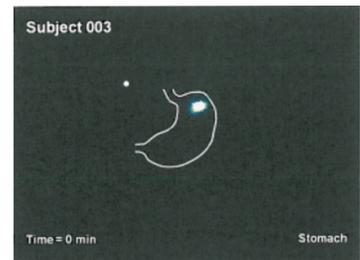


## Protection from Stomach Acidity

Another challenge in probiotic delivery is exposure to stomach acid. Capsugel's DRcaps™ capsules were specifically designed to provide protection from stomach acidity. They are made of HPMC polymer combined with a gelling agent, which is a natural polysaccharide, and resist dissolution in acidic media.

Capsugel evaluated the resistance of DRcaps capsules to acidic media by different methods including *in-vitro* dissolution, *in-vitro* disintegration, *in-vitro* GIT model, and the SHIME method (ProDigest). More importantly, DRcaps capsules were evaluated *in vivo* as well.

A clinical study of DRcaps capsules with eight human subjects confirmed that the capsules did exhibit delayed-release properties. Disintegration started about 52 minutes after ingesting the capsule. For most of the subjects, complete release took place in the small intestine around 20 minutes after the onset of release, when the pH shifted more to a neutral pH of 6.8. These results proved that the DRcaps capsule is clearly acid-resistant and delivers the probiotic to the small intestine where it can work best.<sup>2</sup>



2: DRcaps Capsule Gamma-scintigraphic *in vivo* study, Bio-Images Research, Glasgow, Scotland, 2013.



## Capsules that Facilitate Consumption of Probiotics for Those with Swallowing Difficulties

A probiotic will only be effective if it is actually consumed. For those consumers who find it difficult to swallow—35 percent of general population, some 22 percent of people in long-term care facilities, 45 percent of institutionalized elderly, and 35 percent of adolescents—Capsugel developed the Coni-Snap® sprinkle capsule as an easy-to-open alternative to sticks and sachets. A powdered probiotic—encased in an HPMC capsule for moisture protection that prevents the probiotic’s premature activation—is easily reopened and sprinkled onto food. Using capsules reduces both the number of excipients required and the amount of packaging used.

Evaluation of the Coni-Snap sprinkle capsule’s performance was conducted in two panels, with parents of young children and with elderly persons over 80 years of age but not impaired. The study compared a regular-design capsule with a locking mechanism that makes it more difficult to open with the Coni-Snap sprinkle capsule. Eighty-one percent of all participants found the new design easy to open, giving the Coni-Snap sprinkle capsule a differentiating feature and viable option for those with swallowing difficulties.

DUOCAP® capsule



## DUOCAP® Capsules Deliver for Combination Products

Capsugel’s DUOCAP® capsule technology creates a moisture-defense barrier to prevent water migration in a probiotic internal capsule. This capsule-within-a-capsule is a perfect delivery system for moisture-sensitive compounds. A probiotic-filled inner capsule is suspended in a glycerol-filled external capsule. The water activity of the glycerol and the capsules’ shells is actually lower than the water activity of the encapsulated probiotic—preventing water absorption into the internal capsule.

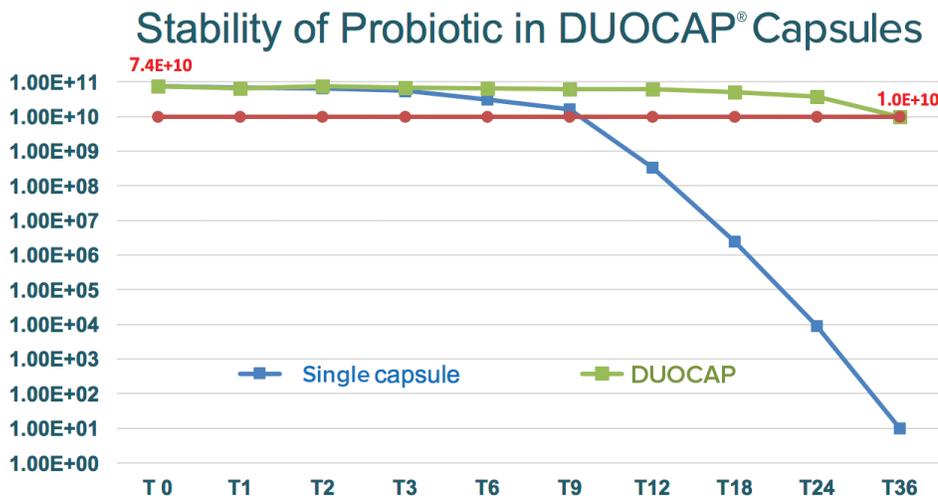
Designed to improve stability and facilitate delayed release, the internal capsule can be a DRcaps™ capsule to further delay the release and delivery of the probiotic to the intestine. This is an ideal solution for Zone IV countries where high heat and humidity often leads to degradation of actives in standard oral dosage forms.

Alternatively, the external capsule could contain vitamin D and/or Vitamin B, as an example, to help address health claims in places like Europe where use of the word “probiotic” is forbidden. Specifically when addressing immunity, more producers are combining probiotics with vitamin C, echinacea or zinc in order to make claims based on those minerals or vitamins.

As proof of concept, Capsugel tested a DUOCAP combination of probiotics in the inner capsule and prebiotics solubilized in the outer capsule. The inner capsule was Vcaps® Plus, size 3, manually filled with Danisco probiotic strain LA-14 200Bio under nitrogen and low humidity conditions (45%Rh). The outer capsule

was a Vcaps® Plus size 00 capsule, filled with the solubilized inulin in glycerol and sealed using LEMS® technology. The study tested two storage environments, one at 4 to 8° C and one at 25° C with a relative humidity of 60%. The test was conducted over 36 months and the finished capsules were packaged in a polypropylene bottle, without a moisture-protection barrier.

The total probiotic count viability was measured by Capsugel's Quality Control department in Colmar, FR. Measurements confirmed the 36-month stability under both storage conditions for the DUOCAP capsules while the standard single capsule only had stability of 9 months. Tests also confirmed that ingredients such as prebiotics and other functional ingredients can be dissolved into the glycerol without impacting the stability of the probiotic capsule. This 36-month stability suggests delivery of a product which retains viability, provides increased value to the consumer and reduces the need for overfill by the probiotic manufacturer.



## Summary

Capsugel's probiotic portfolio includes Vcaps®, Vcaps® Plus and DRcaps™ capsules, which can aid in product shelf life and offers low-moisture solutions to reduce overage in manufacturing. The DRcaps capsule improves delivery of the probiotic to the small intestine and promotes survivability. Capsugel Coni-Snap® sprinkle capsule addresses swallowing issues. Finally, Capsugel DUOCAP® capsule offers synergy enhancement and differentiation in the marketplace.

Solutions	Applications	Polymer
	Increased shelf life can be obtained with low-moisture HPMC capsule	HPMC Low Moisture
	Survival and efficiency: probiotics are protected and delivered to intestine	HPMC
	Alternative to sticks and sachets; solves swallowability issues	Gelatin and HPMC
DUOCAP® 	Synergy enhancement; efficacy in protecting probiotics in presence of other actives	HPMC

Capsugel is a global leader in delivering high-quality, innovative dosage forms and solutions to healthcare companies around the world. Our customers turn to us for the needed science and engineering expertise to bring better medicines and nutritionals to market. As the world's leading provider of empty, two-piece hard capsules and an innovator of ingredient delivery systems, we continue to build on our decades-long track record of quality, reliability, innovation and value creation.

# Capsugel®

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