Technical White Paper: Choosing the Right Active Packaging Solution for Probiotics Requires More than Gut Instinct

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Two of the most critical aspects of probiotic manufacturing and consumption are the potency and stability of the product. There are multiple factors that impact the integrity, and ultimately the efficacy, of probiotics. In this Technical White Paper, we will explore the specific challenges associated with the various processes required to produce probiotic products including formulation, fermentation, strain strength and environmental control. In addition to reviewing best practices in the supply chain, we will share the latest innovations in active packaging and discuss their impact on strain activity and stability. We will present proprietary data from UAS Labs and Merical to demonstrate the efficacy of active packaging solutions that provide an opportunity to reduce the overage manufacturers typically add to meet product label claims. Finally, we will shed some light on the most recent regulatory guidelines that will have a direct impact on the probiotic market.

The Probiotic Journey: From Strain to Shelf

The integrity of a probiotic product starts with the strain providers, formulators, and the final packaging which marks the final step to maintain the viability of the probiotic product. Ineffective packaging can cause degradation, destabilizing the formulation, which in turn affects performance, particularly at the end of shelf life. This is an inherent challenge brands must resolve to ensure products maintain their therapeutic value and meet their stated label claims in terms of potency.

Currently, manufacturers go to extraordinary lengths to mitigate against this loss of potency, typically by adding significant overage, which can be costly. More product in each dose means more cost to package and manufacture.

The use of probiotic health supplements has been an undoubted success story

In the U.S., the use of probiotics quadrupled in the five years to 2012[1] and it has sustained an upward trajectory both in that territory and across the world. At a global level, the market for probiotics is projected to reach a value of around $73 billion by 2024, based on an estimated compound annual growth rate (CAGR) of 7%.[2]

Consumers continue to believe in the promise of probiotics, particularly in relation to gastrointestinal health, keeping a healthy heart, reducing symptoms of certain allergies and Eczema, lactose intolerance, and to boost the immune system. Significant research is underway to explore other uses of probiotics in different populations and to potentially prevent disease onset or progression.

A maturing growth-market

With this strengthening demand, consumers have become more knowledgeable about the qualities and characteristics of particular probiotics as they look to extract the maximum available benefits. Terminology like colony-forming units (CFUs), once perhaps a specialist technical term, is now increasingly familiar to a more knowledgeable audience of probiotic users.

As the market has matured, these consumers are keen to know that labeling claims regarding the quantity of live microbial cells available from their chosen supplement are not only accurate, but sustained over the product's entire shelf life.

In order for probiotic manufacturers and their partners within the supply chain to deliver on these claims, they must manage a complex mix of

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scientific, environmental and commercial factors. In handling live microorganisms, they must minimize any product degradation caused by exposure to heat and moisture vapor over time. This requires a high degree of knowledge and a unique set of skills and experience to make it work within a financially viable framework.

Managing product stability

Probiotic product stability is a key consideration that begins at the initial point of strain selection and formulation. During the manufacturing phase, companies must balance the demands associated with a specific strain and ensure the process results in a stable product that maintains potency over time.

Under the close control of good manufacturing practices (GMP) and incorporating best practices as proposed by the International Probiotics Association (IPA), probiotics companies must consider several variables that can influence the properties of the product in question. The IPA actively advocates for the safe and efficacious use of probiotics throughout the world, with one of its stated objectives being to promote the highest manufacturing standards and science behind probiotics.

Audits provide manufacturers with third-party evidence that production facilities adhere to applicable FDA and United States Pharmacopeia (USP) GMP requirements, and that products meet standards for stability and match shelf-life claims around potency.

Test and release

Producers must maintain tight control of ambient temperature (<25°C) and relative humidity (RH) (<50% preferably <40%) throughout the entire manufacturing process, from blending to encapsulation to packaging. Ambient temperature and RH requirements may differ depending on the process undertaken (i.e. blending vs. packaging). Manufacturers must complete a series of quality control tests on the finished product prior to release into the supply chain and have data available to support stability and shelf-life determinations. These tests should also show the product meets the quality control requirements for microbial purity.

Water Activity (Aw) levels directly impact CFU count and manufacturers use Aw to model product quality over time. Moisture vapor reacts with the product and acts as a catalyst to begin the degradation process. Effectively managing Aw within the package is critical for maintaining quality throughout the entire supply chain, from transport, to storage, to the retail shelf and ultimately to consumers' homes.

Tackling the issue

Manufacturers can implement multiple measures to mitigate degradation and maintain product quality throughout the distribution channel. One measure is to add "overage" of the microbial strains above and beyond higher-than-advertised CFU counts, ranging anywhere from 2x to 10x, in order to account for and manage expected declines in stability and quality over the full shelf-life of the product.

This solution may be effective, but it is clearly not efficient and may not be cost effective. More importantly, this approach may raise regulatory concerns as regulators raise the bar to protect consumer interest. This workaround highlights a clear disparity between claimed and actual CFU levels that, while not harmful to consumers, does not necessarily align with their understanding of the product as described on the product label. There are also hugely significant negative implications from a commercial perspective, as high levels of the active product are effectively 'given away' to compensate for relatively high rates of decline. As such, there is a need for fresh thinking to address this issue.

Rethinking Probiotic Packaging with 3-Phase Activ-Polymer™ Technology

Manufacturers can now take far greater control over the shelf-life stability of their product in a way that provides strong label claim justification and ensures compliance with existing cGMP manufacturing

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3-Phase Activ-Polymer™ Technology

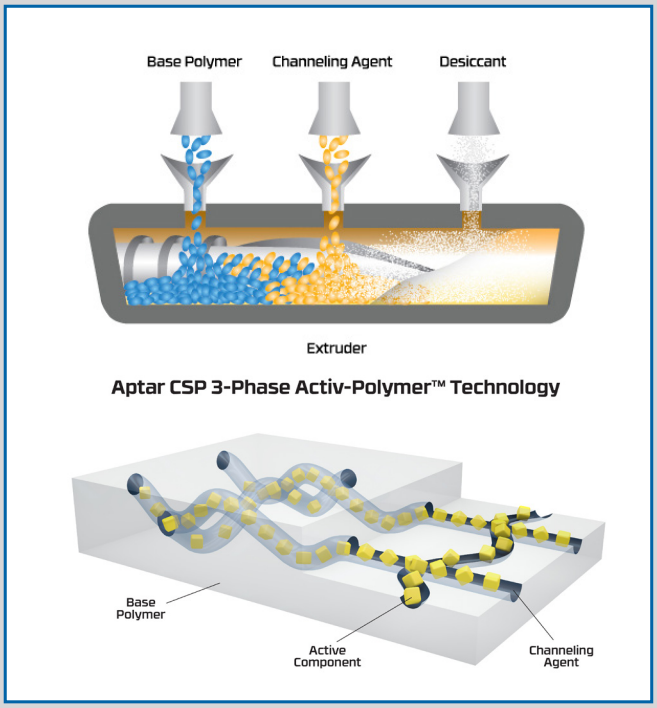

Figure 1: Aptar CSP Technologies' 3-Phase Activ-Polymer™ technology

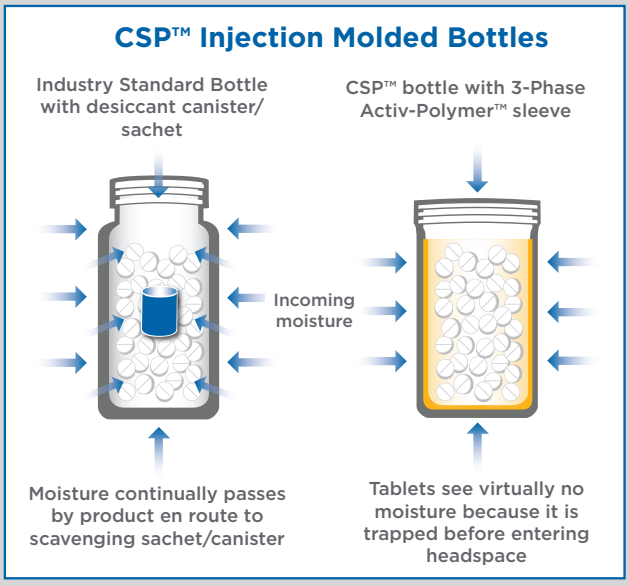

Figure 2: Aptar CSP™ Activ-Bottle vs. industry standard

processes. Leveraging 20 years+ of material science expertise, Aptar CSP Technologies' has developed a unique, material science driven active packaging solution that leverages its proprietary 3-Phase Activ-Polymer™ technology (Figure 1). This technology enables control of the kinetics of moisture adsorption to protect probiotic formulations from residual and external moisture and mitigate the harmful effects of elevated water activity.

Aptar's CSP™ Activ-Vials™ and CSP™ Activ-Bottles resemble current probiotic packaging, but their design incorporates an engineered, non-removable 3-Phase Activ-Polymer™ sleeve (Figure 2). This unique solution reduces initial water activity levels and provides a mechanism for actively controlling moisture to ensure product stability and minimize the loss of potency over time.

A series of tests conducted by UAS Labs, a leading probiotic manufacturer headquartered in Wisconsin, highlights the impact that Aptar CSP's active packaging has on probiotic stability over time. Analysis of the total viable cell count (TVCC), measured in billions of CFU per capsule, showed that the decline in potency after two years was markedly lower for probiotic capsules packaged in CSP™ Activ-Vials than those using aluminum blister packs for product stored at 25°C (77°F) and 60% RH and 30°C (86°F) and 65% RH (Figure 3).

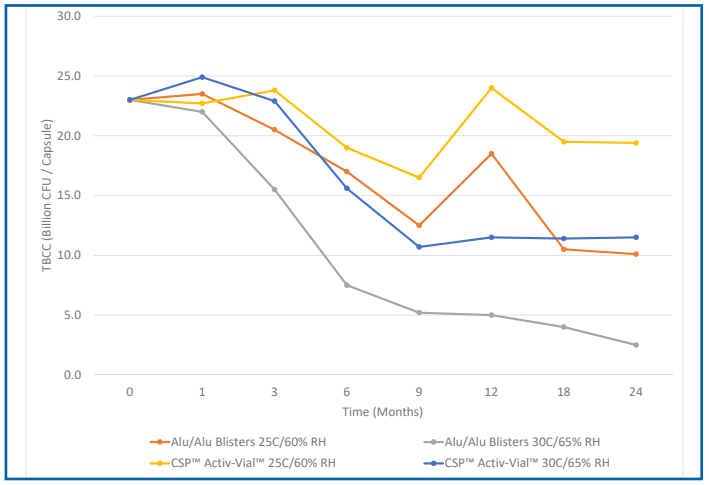

Figure 3: Probiotic Capsule - Potency (CSP™ Activ-Bottle vs. Alu/Alu Blisters)

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For both sets of packaging conditions, the product within aluminum blister packs registered increases in water activity over the first six months, and overall levels were higher at the end of the test period. In contrast, product contained within vials using 3-Phase Activ-Polymer™ technology (CSP™ Activ-Vial™) recorded steep declines in water activity over the first month and remained lower throughout the entire test period (Figure 4).

In a further series of tests, UAS Labs analyzed probiotic capsules with cranberry powder and compared the performance of CSP™ Activ-Vials versus an amber glass bottle with a desiccant canister in varying temperatures and humidity conditions. In all tests, the CSP™ Activ-Vial™ clearly outperformed its glass competitor, registering an overall decrease in water activity rather than an increase, while also limiting any decline in potency (Figures 5 & 6).

A timely opportunity for probiotics manufacturers

Vials and bottles utilizing active packaging technology present a timely opportunity for probiotics brands as they seek to reinforce consumer confidence through greater transparency of product information. The evidence presents a strong justification for adopting smarter, effective, active packaging. In addition, CSP™ Activ-Bottles maintain a consistent packaging format relative to current bottles, and can run on existing packaging lines without significant reconfiguration costs.

This solution also provides a real opportunity to develop new sales channels. Brands can target online sales and less temperature-controlled outlets with confidence as new channels to market, where historically they weren't viable options due to the heightened risk of the product not meeting label claims due to loss of potency.

3-Phase Activ-Polymer™ Technology for Blister Configurations

Aptar CSP's 3-Phase Activ-Polymer™ technology can also be applied in a flexible film format. This form factor enables manufacturers to integrate the technology into traditional blister packaging to create an Activ-Blister™ solution. In the Activ-Blister™ configuration, a manufacturer applies

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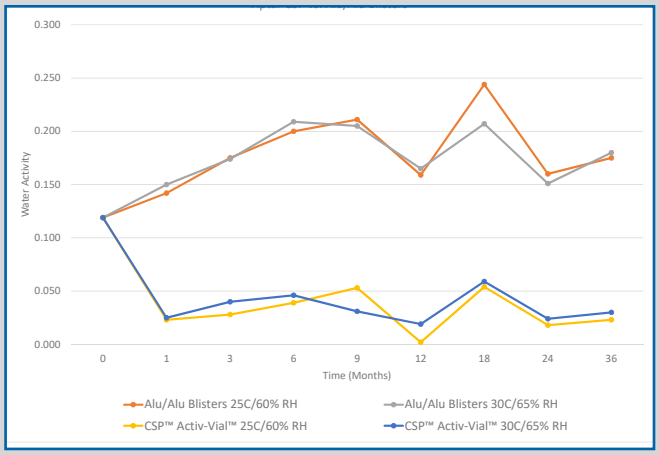

Figure 4: Probiotic Capsule - Water Activity (CSP™ Activ-Vial™ vs. Alu/Alu Blisters)

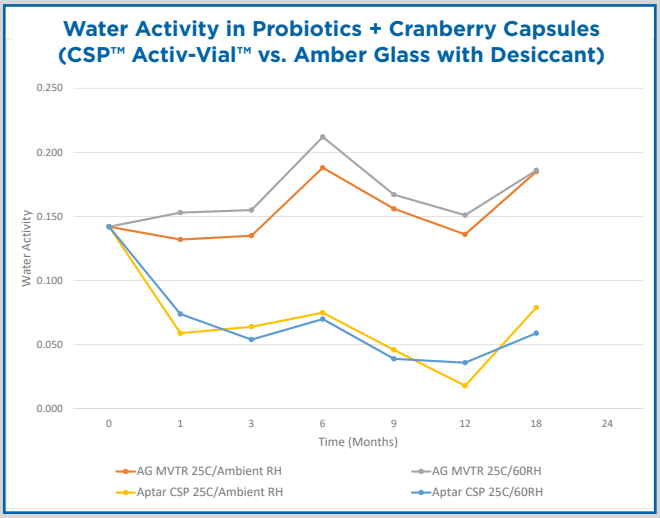

Figure 5: Probiotic Capsule - Water Activity in Probiotics + Cranberry (CSP™ Activ-Vial™ vs. Amber Glass with Desiccant)

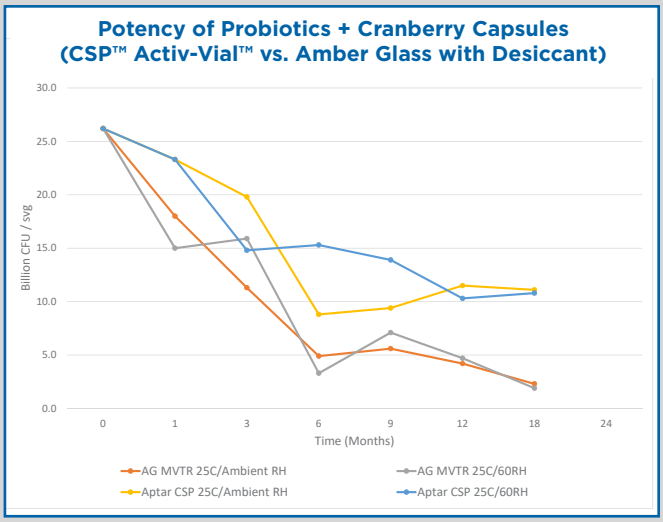

Figure 6: Probiotic Capsule - Potency of Probiotics + Cranberry (CSP™ Activ-Vial™ vs. Amber Glass with Desiccant)

CSP's Activ-Film™ material onto the foil lid stock of a blister pack directly on the blister packaging line (Figure 7). Aptar CSP worked with Merical, a major probiotic contract manufacturer with operations in California and Utah, to conduct a stability study in thermoformed blister packs with and without CSP's Activ-Film™ technology.

As evidenced in Figures 8 and 9, the inclusion of CSP's Activ-Film™ material enabled Merical to reduce the water activity level and maintain the CFU count for a multi-strain probiotic product with a 10 Billion CFU claim. Dr. Jeremy Bartos, Sr. VP, R&D Merical, conducted the evaluation and noted the following: "The results from our stability evaluation with CSP's Activ-Film™ are very exciting. This data set clearly demonstrates the ability to reduce water activity (Aw) and improve probiotic stability within a PVC.PvdC blister pack by adding CSP's Activ-Film™ material. While we have conducted multiple studies that demonstrate the superiority of CSP's 3-Phase Activ-Polymer™ rigid containers relative to traditional rigid packaging options, this is the first study we have conducted to prove that CSP's Activ-Polymer™ technology can also improve blister packaging for probiotics. This presents exciting opportunities for product formulators and brands to develop new products, extend shelf-life, and ensure product integrity across various climate zones."

Regulatory Considerations

Depending on the intended use of a probiotic (drug vs. dietary supplement), regulatory requirements differ greatly and this could become a key feature for discussion in the near future. In September 2018, the FDA issued draft guidance for the industry on quantitative labeling of dietary supplements containing live microbials, which discusses the potential for including details on CFU count within the Supplement Facts label, in addition to the weight declaration required by regulation.[3]

Within the guidance, the FDA acknowledged the role that declaring CFUs would have in promoting confidence if labels specified the number of viable microorganisms throughout the shelf life of the product. The FDA concluded that it intends to exercise enforcement discretion for firms that choose to declare the quantitative amount of live microbial ingredients in the Supplement Facts

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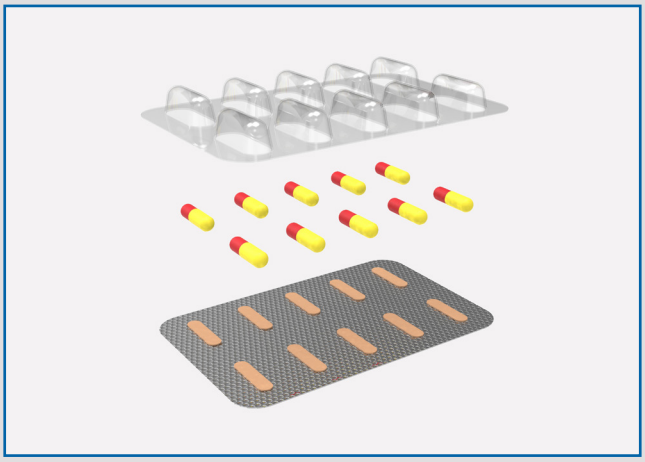

Figure 7: Activ-Blister™ Solutions Illiustration
(CSP™ Activ-Film™ heat staked to foil lid stock)

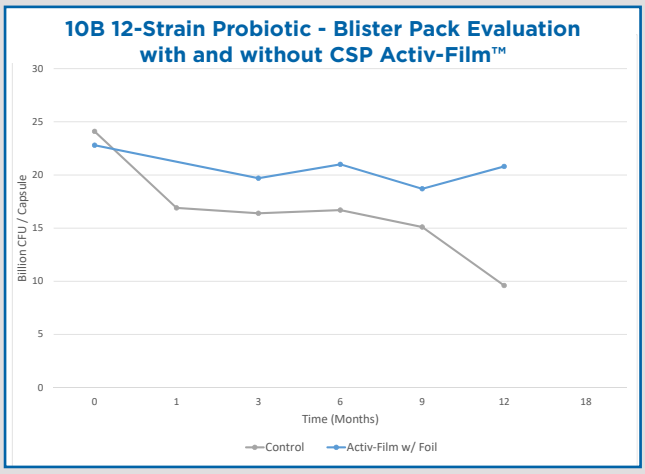

Figure 8: Probiotic Capsule - Potency (Standard Blister Packaging vs. Activ-Blister™ Packaging with CSP™ Activ-Film™)

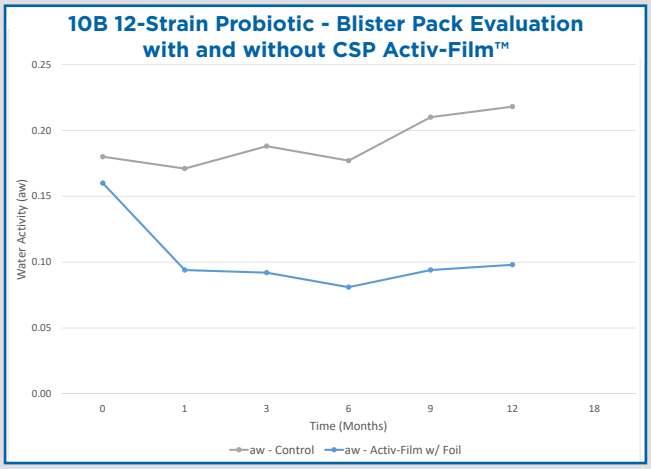

Figure 9: Probiotic Capsule - Water Activity (Standard Blister Packaging vs. Activ-Blister™ Packaging with CSP™ Activ-Film™)

label by CFUs in addition to weight, provided a series of conditions are met, including separating out the information from weight and ensuring that CFUs measures 'only live microbial ingredients and does not include inactive, dead, or nonviable organisms.'[4]

Regulatory Consideration / Validating product quality

The probiotic regulatory landscape is evolving rapidly, and the FDA's decision to allow CFU data to be included on the label is a step that will likely drive the market to meet this new quality standard. The FDA guidance released in September 2018 makes it clear they will focus on this in the future. Potency and stability of the probiotic will be the two most important factors regulators and consumers will use to judge the quality of a probiotic product.

The most recent FDA guidelines also acknowledge that consumers would benefit from permitting the label of dietary supplement products to state the quantity of live microbial dietary ingredients in the Supplement Facts label in terms of CFUs. They also indicated that the CFUs' label claims will be the basis of their enforcement.[5]

The good news is that industry leaders and consumer groups are aligned to build confidence in the quality of probiotics and to encourage growth. With a trend for probiotics brands to develop more complex and more potent products, there are growing calls within the industry and among consumer groups for greater transparency in relation to potency. In this context, CFU data provides clear, official substantiation of product quality and stability over time, including at the end of shelf-life.

In California, policymakers are even pushing for regulation to make this the case. Assembly member Dr. Bill Quirk put forward CA bill AB1178, which initially listed a requirement for probiotics to state the total estimated count of live organisms, but has since been pared back to a declaration of the genus, species, and strain. Ultimately, if it were to be passed, the bill would satisfy consumers and manufacturers in California, but it would also open the door to a scenario where probiotic labeling varies from state to state. As we know as California goes, so does the rest of the country.

Arguably, any confusion or product quality problems have the potential to negatively influence the robust level of demand driving growth for probiotics brands, placing even greater importance on the need for clarity and consistency in relation to potency claims. By optimizing the combination of product and packaging, manufacturers can continue to build trust among consumers actively managing their own health.

References:

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[2] https://www.prnewswire.com/news-releases/the-global-probiotics-market-size-is-expected-to-reach-73-8- billion-by-2024--rising-at-a-market-growth-of-7-7-cagr-during-the-forecast-period-300850278.html

[3] https://www.fda.gov/food/cfsan-constituent-updates/fda-issues-draft-guidance-labeling-dietary-supplements-containing-live-microbials

[4, 5] https://www.fda.gov/media/115730/download

Additional Resources:

International Probiotics Association: http://internationalprobiotics.org/
U.S. Food & Drug Administration: https://www.fda.gov/