Probiotic Packaging

Protecting product potency and stability

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Two of the most critical aspects of probiotic manufacturing and consumption are preserving the potency and stability of the product. Multiple factors can impact the integrity, and ultimately the efficacy, of probiotics. In this article, we explore the specific challenges associated with the various processes required to produce probiotic products, including challenges regarding formulation, fermentation, strain strength, and environmental control.

In addition to reviewing best practices in the supply chain, we provide an example of the latest innovations in active packaging and discuss their impact on strain activity and stability. Active packaging employs material science technology to create an engineered microclimate environment to ensure product integrity. Active packaging technology can be applied to control moisture, scavenge oxygen or volatile organic compounds (VOCs), emit or remove aromas, or serve as an antimicrobial agent.

Finally, we shed some light on the most recent regulatory guidelines that will have a direct impact on the probiotic market. We discuss why packaging that preserves the quality of probiotic ingredients will become increasingly important in this regulatory environment.

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The Probiotic Journey: From Strain to Shelf

The integrity of a probiotic product starts with the strain providers, formulators, and final packaging that 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 manufacture.

Probiotic Health Supplements: An Undoubted Success Story

In the U.S., the use of probiotics quadrupled in the five years leading up to 2012[1], and the market has sustained an upward trajectory both domestically and abroad. 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, managing lactose intolerance, and boosting 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.

For probiotic manufacturers and their partners within the supply chain to deliver on these claims, they must manage a complex mix of 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 (GMPs) and incorporating best practices as proposed by the International Probiotics Association (IPA; http://internationalprobiotics.org), 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 (e.g., 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 2× to 10×, in order to account for and manage expected declines in stability and quality over the full shelf life of the product.

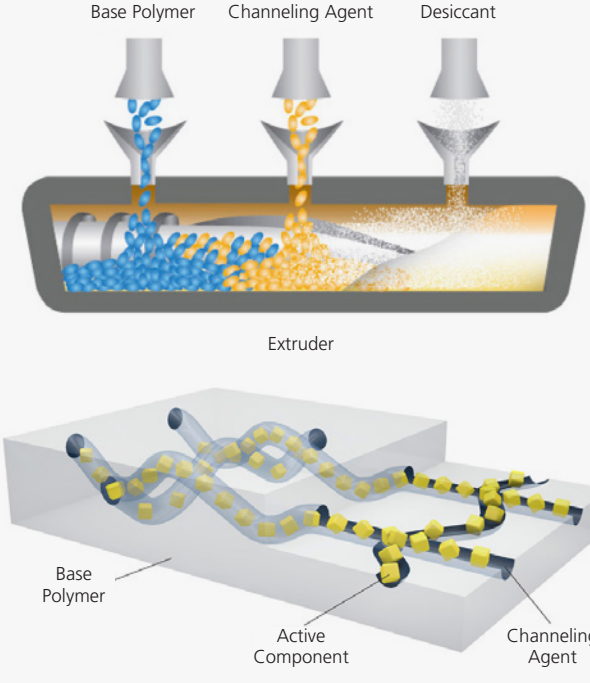
This solution may be effective, but it is clearly not efficient and may not be cost-effective. More importantly, this approach may raise regulatory concerns as regulators raise the bar to protect consumer interest. This workaround highlights a clear disparity between claimed and actual CFU levels that, while not harmful to consumers, does not necessarily align with their understanding of the product as described on labels. 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

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 GMP manufacturing processes: by seeking advanced protective packaging solutions.

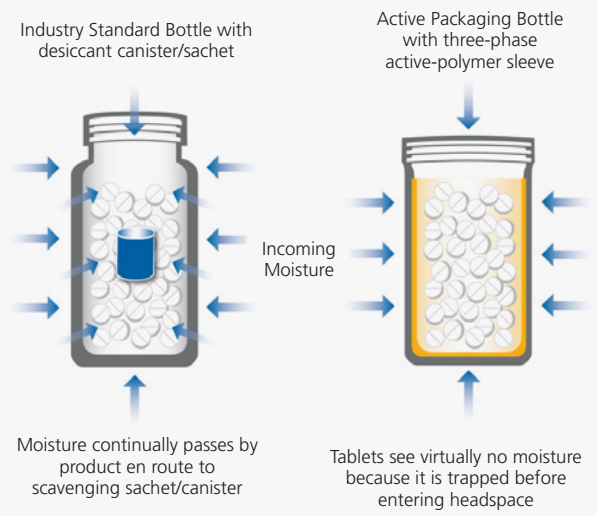
One example of such an approach involves a material science–driven active packaging solution that leverages a proprietary 3-Phase Activ-Polymer technology. Disclosure: This technology was developed by the co-author's company, Aptar CSP Technologies (Auburn, AL). This technology enables control of the kinetics of moisture adsorption to protect probiotic formulations from residual and external moisture, and mitigate the harmful effects of elevated water activity. (Figure 1)

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



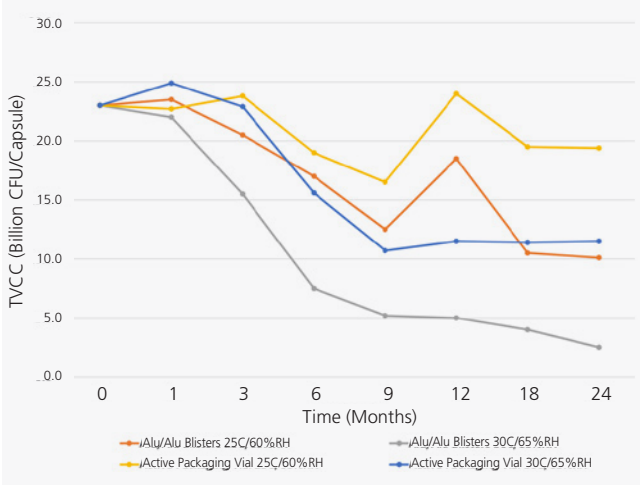
The active packaging resembles current probiotic packaging but can, for instance, incorporate an engineered, non-removable three-phase active-polymer sleeve. (This can be applied to vials, bottles, or blisters.) This solution reduces initial water activity levels and provides a mechanism for actively controlling moisture to ensure product stability and minimize loss of potency over time. (Figure 2)

Figure 2: Active Packaging Bottle vs. Industry Standard



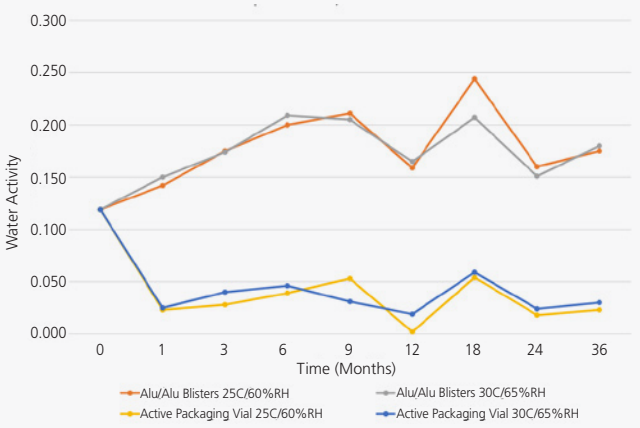
A series of tests conducted on this technology by probiotic manufacturer UAS Labs (Madison, WI) highlights the impact that this type of active packaging can have on probiotic stability over time. Analysis of the total viable cell count (TVCC), measured in billions of CFU per capsule, showed that the decline in potency after two years was markedly lower for probiotic capsules packaged in these active packaging 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
(Active Packaging Vial vs. Alu/Alu Blisters)



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. However, product contained within the active packaging vials recorded steep declines in water activity over the first month and remained lower throughout the entire test period. (Figure 4)

Figure 4: Probiotic Capsule - Water Activity
(Active Packaging Vial vs. Alu/Alu Blister)



In a further series of tests, probiotic capsules with cranberry powder were tested in various packaging formats—active packaging vials versus an amber glass bottle with a desiccant canister—in varying temperatures and humidity conditions. In all tests, the active packaging vial outperformed its glass competitor, registering an overall decrease in water activity rather than an increase, a comparably favorable moisture vapor transmission rate (MVTR), and an ability to limit any decline in potency. (Figures 5 & 6)

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

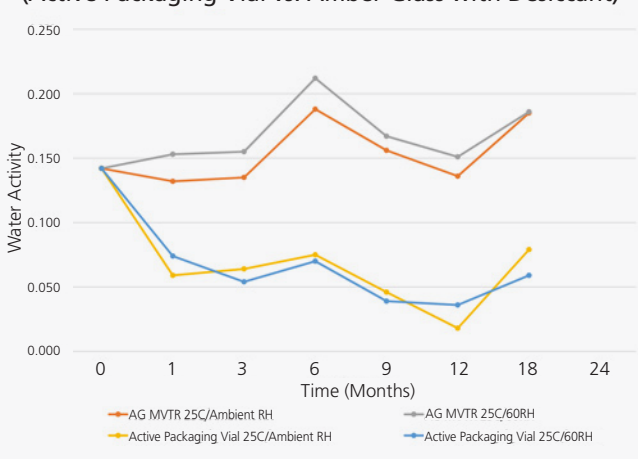
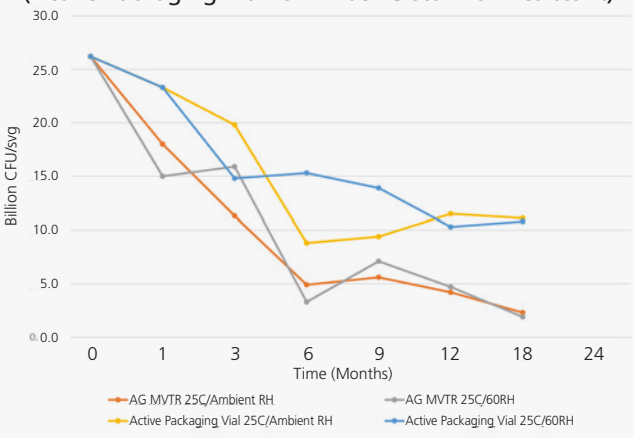


Figure 6: Probiotic Capsule - Potency of Probiotics + Cranberry (Active Packaging Vial vs. Amber Glass with Desiccant)



A Timely Opportunity for Probiotics Manufacturers

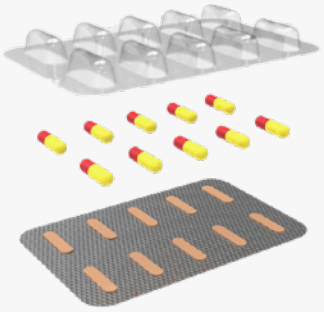
Vials and bottles utilizing active packaging technologies present a timely opportunity for probiotics brands as they seek to reinforce consumer confidence through greater transparency of product information. The evidence presents a strong justification for adopting smarter, effective active packaging. Depending on the active packaging system used, the switch is typically hassle-free: for example, active packaging bottles may maintain a consistent packaging format relative to current bottles and can run on existing packaging lines without significant reconfiguration costs.

Solutions like these also provide 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 those channels weren't viable options due to the heightened risk of the product not meeting label claims due to loss of potency.

Active Packaging Technology for Blister Configurations

Active polymer technologies can also be applied in a flexible film format. This form factor enables manufacturers to integrate the technology into traditional blister packaging. In an active packaging blister configuration, a manufacturer would apply an active film material onto the foil lid stock of a blister pack directly on the blister packaging line. (Figure 7)

Figure 7: Active Packaging Blister Solution Illustration (Active film material heat staked to foil lid stock)



The co-author's company, Aptar CSP, recently worked with MeriCal (Orange, CA), a probiotic contract manufacturer with operations in California and Utah, to conduct a stability study in thermoformed blister packs with and without active blister film technology. As evidenced in Figures 8 and 9, the inclusion of the active blister film material enabled MeriCal to reduce the water activity level and maintain the CFU count for a multistrain probiotic product with a 10-billion-CFU claim. Dr. Jeremy Bartos, senior vice president of R&D for MeriCal, conducted the evaluation and noted the following: "This data set clearly demonstrates the ability to reduce water activity (Aw) and improve probiotic stability within a blister pack. This presents exciting opportunities for product formulators and brands to develop new products, extend shelf life, and ensure product integrity across various climate zones."

Figure 8: Probiotic Capsule - Potency (Standard Blister Packaging vs. Blister Packaging with Active Film Material)

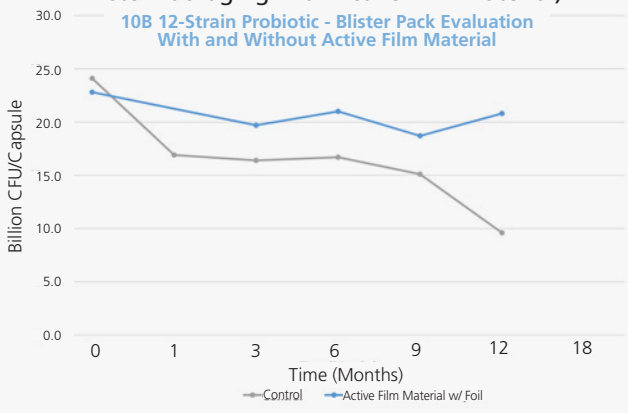
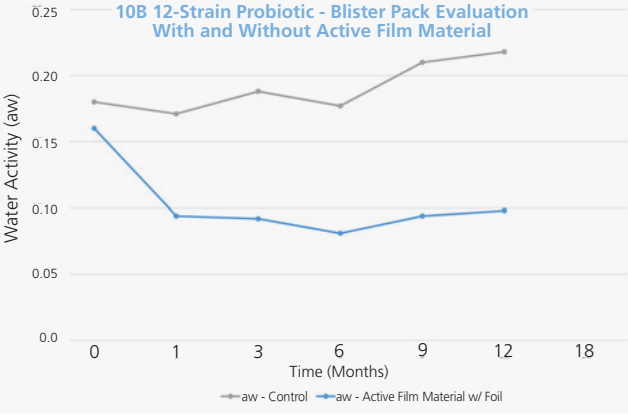


Figure 9: Probiotic Capsule - Water Activity (Standard Blister Packaging vs. Blister Packaging with Active Film Material)



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, FDA issued draft guidance for the industry on quantitative labeling of dietary supplements containing live microbials, which

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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, FDA acknowledged the role that declaring CFUs would have in promoting consumer confidence if labels specified the number of viable microorganisms throughout the shelf life of the product. 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 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 measure "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 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 the agency 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.[4]

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. Assemblymember Dr. Bill Quirk put forward CA bill AB 1178, 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. N

Billy Abrams *has been with Aptar CSP Technologies (Auburn, AL) for 24 years and has worked in operations, program management, and business development. He has worked on probiotic packaging initiatives for over 15 years and has commercialized countless projects utilizing CSP's Activ-Polymer technology across a range of application fields with major global pharmaceutical, diagnostic, and nutritional supplement companies.*

Greg Leyer, PhD, *has dedicated his professional career to probiotic advancement, making him not only a critical component of UAS Labs (Madison, WI) but a world-renowned expert, educator, and speaker in the field. Greg has authored or co-authored 24 publications in the areas of probiotic clinical results, application know-how, and safety parameters, and he holds patents in the field. He holds an MS and PhD in food microbiology and toxicology, respectively, and is an active member of the International Probiotics Association and the International Scientific Association for Probiotics and Prebiotics.*

Badre Hammond's *background is in biochemistry and drug development, with 16 years' experience in pharmaceutical product development, packaging, and drug delivery systems. He has broad experience in managing development of novel drug product programs, from formulation development through preclinical processes and chemistry, manufacturing and controls (CMC), all the way to market launch. As the vice president of commercial operations for Aptar CSP Technologies, his current focus is on commercial best practices, strategy, and business development.*

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